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Efficient synthesis of 5-alkyl amino and thioether substituted pyrazoles

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Abstract—Nucleophilic substitution reactions of 1-(4-methylsulfonyl-2-pyridyl)-5-chloro pyrazoles with various substitutions at the 4 position with amine nucleophiles and thiols occur under mild conditions to provide the 5-alkyl amino and thioether pyrazoles in high yields.

1. Introduction

Many vicinal bis-aryl substituted aryl, heteroaryl, cycloalkyl or heterocyclic templates have been disclosed as cyclooxygenase-2 (COX-2) selective agents.[1a] Two successful templates have been the 1,5-disubstituted pyrazoles and 3,4-disubstituted furanones which have resulted in the commercial products celecoxib (Celebrex®) and rofecoxib (Vioxx®), respectively. A third COX-2 selective agent to come on the market is valdecoxib (Bextra®), which belongs to the isoxazole class. Several other classes of compounds with COX-2 selectivity are still under development.[1b]

We started to look at 1,5-diarylpyrazole analogs as selective COX-2 inhibitors for veterinary use.[2] While we were initiating our efforts in this area, Merck disclosed some phenoxy and alkoxy lactones with improved activity against the COX-2 enzyme.[3] That report prompted us to look at 5-amino, ether and thioether pyrazoles as alternatives to the well known 1,5-diaryl pyrazoles as selective COX-2 inhibitors (Fig. 1). In this paper we report our development of an efficient synthesis of the 5-alkyl amino pyrazoles for our anti-inflammatory program.

Some scattered reports are available where the displacement of the 5-chloro pyrazole seems feasible with hydrazines, thiols, azide, and amines when an electron withdrawing group is present at the 4-position.[4] Little has been investigated on the scope of the amino substitution reaction with the 4-nitrile or ester derivatives.[5] Thus, we decided to explore the amino substitution of the 1-(4-methylsulfonyl-2-pyridyl)-5-chloro-4-cyano pyrazoles with variety of amines to enable us to rapidly synthesize and purifiy analogs.

2. Results and discussion

The desired 5-chloro pyrazoles were synthesized as shown in Scheme 1. The condensation of the 2-pyridyl hydrazine **1**[5] with ethyl trifluoromethyl acetoacetate in ethanol under reflux overnight followed by treatment with sodium hydroxide to effect complete ring closure provided the 5-hydroxy pyrazole **2** in greater than 80% yield. This alcohol resisted complete conversion to the 5-chloro pyrazole **3** (37%) even after prolonged heating with $POCl_3$. Use of literature conditions ($POCl_3$, DMF)

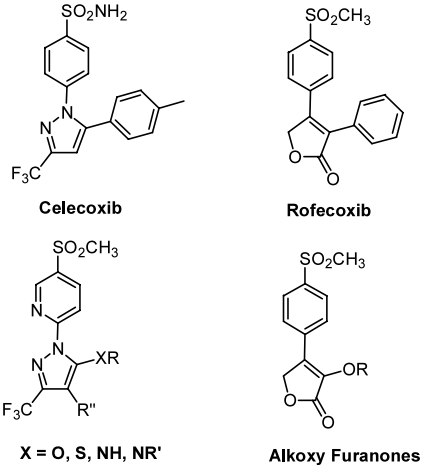

Figure 1. Lead COX-2 inhibitors and synthetic targets.

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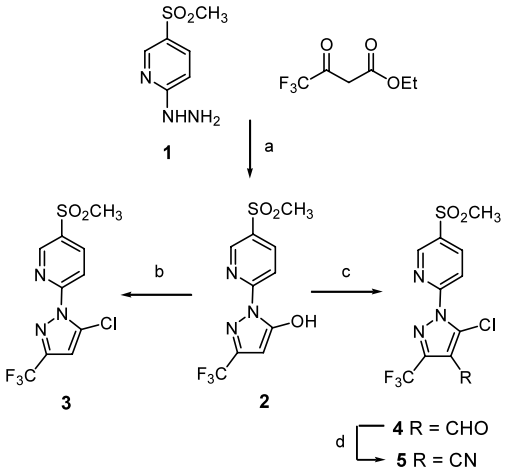
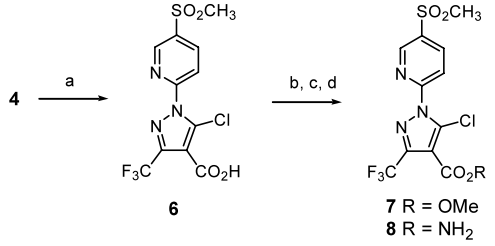
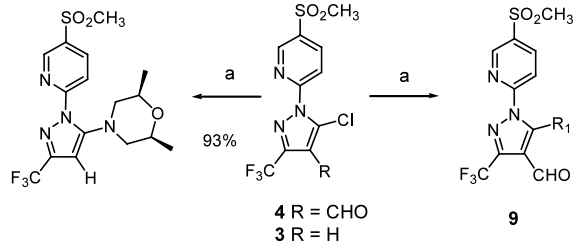


Scheme 1. *Reagents and conditions*: (a) EtOH, reflux, ~16 h; 2 equiv. NaOH, EtOH, 30 min, >90%; (b) $POCl_3$, 120°C, 37%; (c) $POCl_3$, 4 equiv. DMF, 80°C, 4 h; (d) $HONH_2{\cdot}HCl$, TFE, reflux, 2 h, 90%; Cl_3CCOCl, Et_3N, CH_2Cl_2, 0°C, 4–6 h, >90%



Scheme 2. *Reagents and conditions*: (a) 2 equiv. $KMnO_4$, 2 h, 84%; (b) oxalyl chloride, cat. DMF, DCM, 2 h; (c) for **7**: 1.4 equiv. NaOMe, THF, rt, 30 min, 79%; (d) for **8**: NH_3, MeOH, rt, 16 h, 67%.



Scheme 3. *Reagents and conditions*: (a) 1.1–2.0 equiv. of reactant, 1.2–2.0 equiv. of Et_3N, DCM for rt and 40°C; DCE for 80°C.

gave the 4-formyl-5-chloro pyrazole **4** in >90% yields.[6] The aldehyde was reacted with hydroxylamine hydrochloride salt in refluxing trifluoroethanol (TFE) to give the oxime (90%) which was then converted to the desired nitrile **5** (90%) with trichloroacetylchloride in the presence of triethylamine.

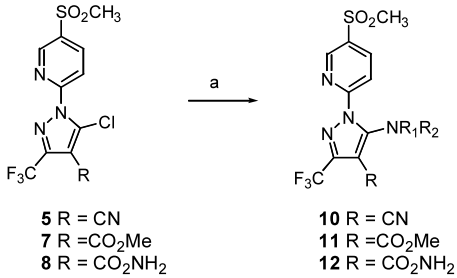
The aldehyde was further oxidized with potassium permanganate to give the acid **6** in 84% yield (Scheme 2). The acid was converted to the acid chloride (oxalyl chloride, catalytic DMF) and trapped with sodium methoxide and ammonia to give the methyl ester **7** (80%) and amide **8** (67%), respectively.

We initially explored the substitution reaction on **4** with various piperazines at room temperature in methylene chloride. To our surprise, the reaction was facile and gave clean products in excess of 95% after aqueous work-up (Scheme 3, Table 1). Similarly, thiophenol reacted at room temperature to provide the product in 98% yield. Imidazole required a temperature of 40°C to provide a 76% yield of the product. For alkyl amines, the temperature had to be increased to 80°C in dichloroethane before complete reaction was seen. No reaction of the amines with the aldehyde was detected under these conditions (Table 1). Reaction of **3** with *cis*-dimethylmorpholine (80°C, DCE) also gave the substitution product in 93% yield (Scheme 3).

For the purposes of studying the scope of the reaction and to make useful analogs as COX-2 inhibitors, these same conditions were extended to make amino analogs of **5** (Scheme 4, Table 2). For the parallel synthesis, we did reactions in 0.2 mM scale with 2 equiv. each of the amine and triethylamine at 80°C for 16–20 h in dichloroethane. Rapid purification was done using batch preparative TLC, washing and filtration of desired product silica bands, followed by solvent evaporation. More than 200 amino analogs were made rapidly following this parallel reaction/purification protocol. Almost all primary amines and most of the secondary cyclic amines underwent the displacement reaction in high yields (Table 2). Dialkyl amines gave variable yields depending on the substituent size and steric bulk.

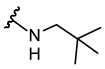
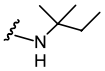
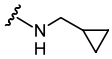
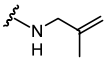
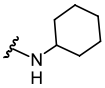
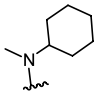
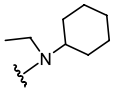
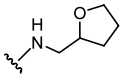
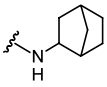
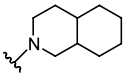
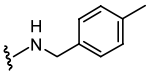
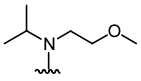
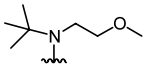
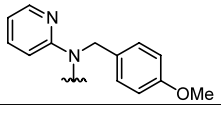
Table 1. Reactions with chloro aldehyde pyrazole **4**

Entry	Reactant	Conditions	% Yield
1	*N*-Ethylpiperazine	rt, 1 h	95
2	*N*-Phenylpiperazine	rt, 2 h	93
3	*N*-Acetylpiperazine	rt, 2 h	94
4	Thiophenol	rt, 2 h	98
5	Imidazole	40°C, 16 h	76
6	Isopropyl amine	40°C, 16 h	14
7	Aminomethyl cyclopropane	80°C, 20 h	66
8	Cyclohexanethiol	80°C, 20 h	73
9	2-Mercaptopyridine	80°C, 20 h	95
10	*N*-Methyl benzylamine	80°C, 20 h	92



Scheme 4. *Reagents and conditions*: (a) 1.2–2.0 equiv. amines, 2 equiv. Et_3N, DCE, 80°C, 0–99%.

Table 2. Amino substitution reaction on 5-chloro-4-nitrile pyrazole **5**

Entry	Amine, R1	%Yield
1.		86
2.		95
3.		69
4.		99
5		63
6.		67
7.		60
8.		34
9.		94
10.		97
11.		60
12.		94
13.		46
14.		24
15.		0
16.		0

Although aryl thiols readily reacted even at room temperature, aryl amines either gave no product or very low yields under these conditions. Even alkyl substituted aryl amines failed to provide products (item 16)

Table 3. Reactions with 5-chloro 4-methylester **7** and amide **8**

Entry	Reactant	R	% Yield
1	2-Methylbutylamine	CO_2CH_3	46
2	3-Amylamine	CO_2CH_3	42
3	2-Methylpiperidine	CO_2CH_3	44
4	Neopentylamine	CO_2CH_3	49
5	Aminomethyl cyclopropane	CO_2CH_3	19
6	Aminomethyl cyclopropane	CO_2NH_2	17
7	*cis*-2,6-Dimethylmorpholine	CO_2NH_2	50
8	Cyclohexane methylamine	CO_2NH_2	33
9	*endo*-2-Amino norbornane	CO_2NH_2	32
10	Piperidine	CO_2NH_2	17

Several analogs of **7** and **8** were also prepared using the same procedure as described above, which indicates a broad generality of this procedure (Table 3). DMF as well as other solvents could be used in the displacement reactions but we chose dichloroethane because of convenience for rapid analog purification and isolation. Since the compounds were synthesized in a small library fashion, none of the reactions have been optimized.

Thus, we have developed a convenient and efficient way of introducing alkyl amines and aryl and alkyl thiols to the 5-position of 1-(4-methylsulfonyl 2-pyridyl) 4-substituted pyrazoles to enable generation of large numbers of analogs for rapid biological screening.[7]

Acknowledgements

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7. Sample reaction procedure (example 10, Table 2): A suspension of **5** (200 mg, 0.570 mmol) in 2 ml dichloroethane (DCE) was treated with triethylamine (0.684 mmol, 1.2 equiv.) and piperidine (0.627 mmol, 1.1 equiv.) and heated the mixture at 80°C for 16 h. TLC shows completion. Water was added to the mixture, shaken and separated using an organic selective membrane filtration cartridge. Solvent was evaporated to give a crude residue. The product (771 mg, 97%) was purified using preparative thin layer chromatography, utilizing 1:1 EtOAc/hexanes for elution. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.07 (d, 1H, $J=2.5$ Hz), 8.40–8.37 (dd, 1H, $J=2.5$, 5.8 Hz), 8.02–8.00 (d, 1H, $J=8.7$ Hz), 3.35–3.32 (t, 4H, $J=5.2$ Hz), 3.16 (s, 3H), 1.72–1.56 (m, 6H). MS (m/z) 400.1 (M+H). All the compounds run in parallel synthesis manner were characterized by LC–MS and are consistent with the structures. Compounds that were scaled up are characterized by ^{1}H NMR and LC–MS. Data for select compounds: entry 9, Table 1: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.97 (s, 1H), 8.93–8.92 (t, 1H $J=1.45$ Hz), 8.39–8.36 (dd, 1H, $J=2.3$, 7.3 Hz), 8.23–8.22 (m, 1H), 8.11–8.08 (d, 1H, $J=8.3$ Hz), 7.62–7.57 (m, 1H), 7.31–7.29 (d, 1H, $J=7.9$ Hz), 7.09–7.06 (m, 1H), 3.11 (s, 3H); MS (m/z) 429.3 (M+H); entry 10, Table 1: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.96 (s, 1H), 9.04 (d, 1H, $J=2.5$ Hz), 8.35–8.33 (dd, 1H, $J=2.5$, 5.8 Hz), 7.88–7.86 (t, 1H, $J=8.3$ Hz), 7.29–7.20 (br, 5H), 4.39 (s, 2H), 3.15 (s, 3H), 2.84 (s, 3H); MS (m/z) 439.2 (M+H); entry 7, Table 2: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.07–9.08 (d, 1H, $J=1.6$ Hz), 8.41–8.39 (dd, 1H, $J=2.3$, 8.5 Hz), 7.98–7.95 (d, 1H, $J=8.5$ Hz), 3.3–3.2 (m, 2H), 3.15 (s, 3H), 3.15 (m, 1H), 2.0–1.0 (m, 13H); MS (m/z) 442.1 (M+H); entry 13, Table 2: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06–9.05 (d, 1H, $J=2.5$ Hz), 8.40–8.38 (dd, 1H, $J=2.5$, 8.3 Hz), 7.99–7.96 (d, 1H, $J=8.7$ Hz), 3.15 (s, 3H), 2.81 (s, 3H), 1.30–1.28 (d, 6H, $J=6.6$ Hz); MS (m/z) 388.1 (M+H).