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Efficient fluoride-mediated synthesis of 5-alkyl amino- and ether-substituted pyrazoles

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Abstract—Fluoride-mediated nucleophilic substitution reactions of 1-(4-methylsulfonyl (or sulfonamido)-2-pyridyl)-5-chloro-4-cyano pyrazoles with various amines and alcohols occur under mild conditions to provide the 5-alkyl amino and ether pyrazoles in moderate to 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,b] 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furanones, which have resulted in the commercial products celecoxib (Celebrex®) and rofecoxib (Vioxx®, recently withdrawn from the market), respectively. A third COX-2 selective agent to come in the market is valdecoxib (Bextra®, recently withdrawn), which belongs to the isoxazole class.[2] Several other classes of compounds with COX-2 selectivity are still under development.[1b]

Our efforts in the search for canine COX-2 selective agents have resulted in a potent and selective COX-2 lead for canine use.[3] To discover both canine and feline COX-2 selective agents, we chose to modify the 5-aryl pyrazole class to 5-heteroatom-substituted pyrazoles (Fig. 1), analogous to the Merck ethers of the furanone class.[4] Our efforts to prepare the 5-amino-substituted pyrazoles led to the development of a novel synthesis of 5-amino pyrazoles.[5] In this letter, we report a fluoride-mediated efficient synthesis of the 5-ether and amino pyrazoles via displacement of the 5-chloro substituent.

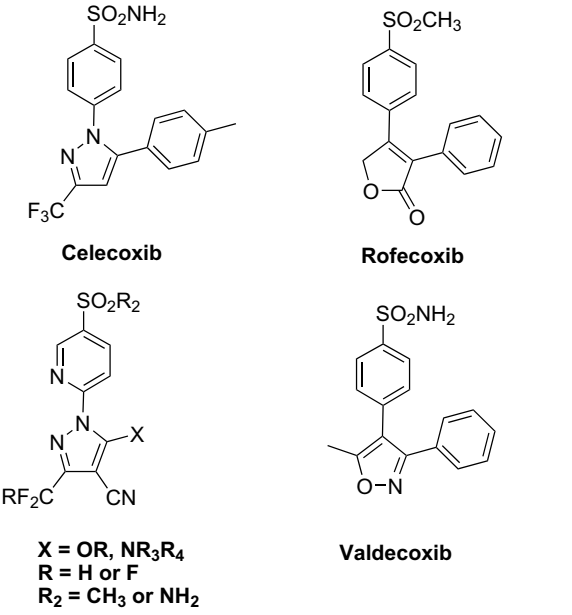

Figure 1. Lead COX-2 inhibitors and synthetic targets.

Some reports are available where the displacement of 5-chloro pyrazole seems feasible with hydrazines, thiols, azide and amines with an electron-withdrawing group present at the 4-position.[6] A few substitution reactions of 5-halogen pyrazoles with strong alkoxides have also been reported to date.[7] Fluoride-mediated reactions, either by itself or in conjunction with alumina, are commonly used in SN2 displacements and aromatic

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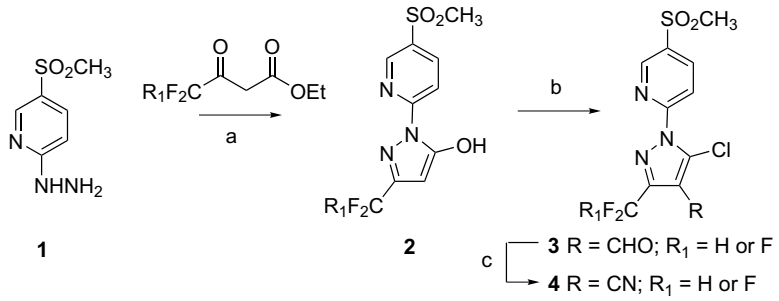
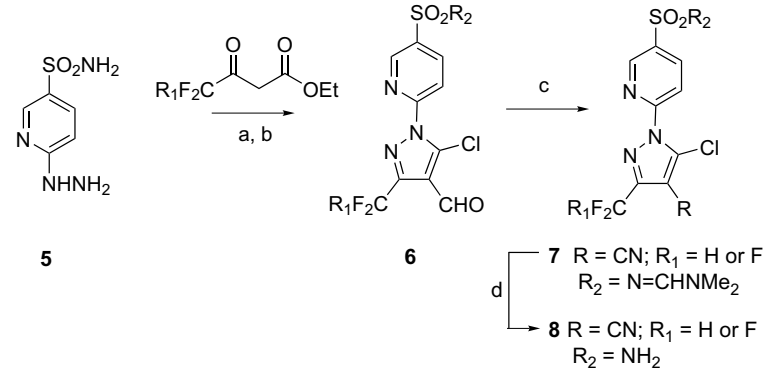
halide substitution reactions with amines, thiols and alcohol nucleophiles.[8] Thus, this fluoride-mediated synthesis was found to be applicable to our system, readily amenable to parallel synthesis, and represents a very mild alternative to prepare 5-ether and -amino pyrazoles in a rapid manner.

2. Results and discussion

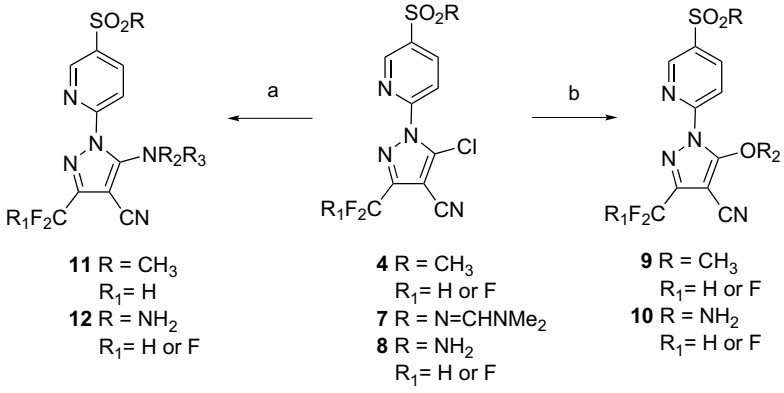
The desired 5-chloro pyrazoles **4**, **7** and **8** were synthesized as shown in Schemes 1 and 2. The condensation of 2-pyridyl hydrazine **1** with ethyl trifluoromethyl acetoacetate in ethanol under reflux overnight, followed by treatment with sodium hydroxide to effect complete ring closure, provided the pyrazolone **2** in greater than 80% yield. Under identical conditions, the difluoroacetoacetate gave very poor yields. Addition of ammonium chloride and refluxing in isopropanol provided the desired 3-difluoromethyl pyrazolone **2** in good yields. The treatment of **2** with $POCl_3$ and DMF gave the 4-formyl-5-chloro pyrazole **3** in >90% yields for both the 3-trifluoro and 3-difluoro-substituted pyrazoles.[9] The



Scheme 1. Reagents and conditions: (a) For $R_1 = F$, EtOH, reflux, ~16 h; for $R_1 = H$, *i*PrOH, NH_4Cl, reflux, ~16 h; 2 equiv NaOH, EtOH, 30 min, >80% for $R_1 = F$; 50–70% for $R_1 = H$; (b) $POCl_3$, 4 equiv DMF, 80 °C, 4 h, 60–80%; (c) $NH_2OH{\cdot}HCl$, TFE, reflux, 2 h, 90%; Cl_3CCOCl, Et_3N, CH_2Cl_2, 0 °C, 4–6 h, >90%.



Scheme 2. Reagents and conditions: (a) For $R_1 = F$, EtOH, reflux, ~16 h; 2 equiv NaOH, EtOH, 30 min, >80%; for $R_1 = H$, *i*PrOH, NH_4Cl, reflux, ~16 h; (b) $POCl_3$, 4 equiv DMF, 80 °C, 4 h; (c) $NH_2OH{\cdot}HCl$, TFE, reflux, 2 h, 90%; Cl_3CCOCl, Et_3N, CH_2Cl_2, 0 °C, 4–6 h, >90%; (d) 1 N HCl/THF, 50 °C.



Scheme 3. Reagents and conditions: (a) 1.1–2.0 equiv amine, 2.0 equiv of KF, DMSO, rt; (b) 1.1–2.0 equiv alcohol, 2.0 equiv of KF or CsF, DMSO, rt; 1 N HCl/THF, 50 °C.

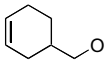
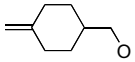
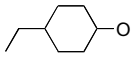
aldehyde **3** was reacted with hydroxylamine hydrochloride salt in refluxing trifluoroethanol (TFE) to give the oxime (90%), which was then converted to the desired nitrile **4** (90%) with trichloroacetylchloride in the presence of triethylamine (Scheme 2).

Similarly, the sulfonamide pyridyl hydrazine **5** was reacted with ethyl trifluoromethyl and difluoromethyl acetoacetate to give the pyrazolones, which were subsequently converted to the aldehyde **6** in very good yields (Scheme 3). During this step, the sulfonamide is also protected as the amidine derivative. The aldehyde **6** is then converted to the nitrile **7** as before. The free sulfonamide **8** was isolated by heating the amidine derivative **7** to 50 °C in aqueous acid.

We initially explored the substitution reaction on **4** with various alcohols. The treatment of the chloride **4** with excess alcohol in the presence of 2 equiv of solid KF or CsF in DMSO at room temperature provided **9a**–**k** in moderate to good yields (Table 1).

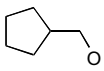
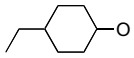
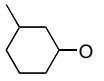
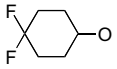
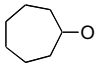
The reactions were run in a parallel manner in a shaker and purified by HPLC or preparative TLC after aqueous workup. For some of the more hindered alcohols, CsF provided better yields compared to KF (**9d**,**h**).

Table 1. Ether pyrazoles **9**

Entry	OR_2	Base	R_1	R	Yield[a] (%)
9a		KF CsF	F	CH_3	14 58
9b		KF	F	CH_3	27
9c		KF	H	CH_3	47
9d		KF CsF	F	CH_3	39 55
9e		KF	F	CH_3	68
9f		KF	F	CH_3	60
9g		KF CsF	F	CH_3	Trace 24
9h		KF CsF	F	CH_3	Trace 26
9i		KF	H	CH_3	32
9j		KF	H	CH_3	28
9k		KF	H	CH_3	44

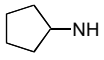
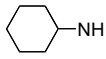
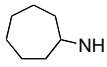
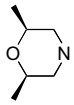
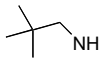
[a] Unoptimized yields based on 0.2 mmol scale parallel synthesis.

Table 2. 5-Ether pyrazoles **10**

Entry	OR_2	Base	R_1	R	Yield[a] (%)
10a		CsF	F	NH_2	39
10b		CsF	F	NH_2	47
10c		CsF	F	NH_2	34
10d		CsF	F	NH_2	25
10e		CsF	F	NH_2	14
10f		CsF	F	NH_2	5.3

[a] Unoptimized yields based on 0.2 mmol scale parallel synthesis.

Table 3. 5-Amino substitution products **11**

Entry	NR_3R_4	Base	R_1	R	Yield[a] (%)
11a		KF TBAF[b]	H	CH^3	84 54
11b		KF	H	CH_3	93
11c		KF	H	CH_3	>98
11d		KF TBAF[b]	H	CH_3	98 41
11e		KF	H	CH_3	96
11f		KF	H	CH_3	>98
11g		KF	H	CH_3	92
11h		KF	H	CH_3	97
11i		KF	H	CH_3	96
11j		TBAF[b]	H	CH_3	50

[a] Unoptimized yields based on 0.2 mmol scale parallel synthesis.
[b] TBAF/DCM, rt.

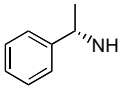
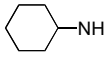
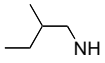
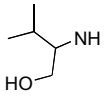
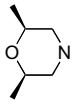
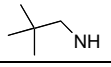
Similar reaction results were obtained for both the trifluoromethyl- and difluoromethyl-substituted pyrazoles (**9i–k** vs **9a–h**).

Attempts at reacting the alcohols under similar conditions with free sulfonamide **8** did not lead to any desired products. The protected sulfonamide derivative **7**, however, gave the desired ethers in modest yields (Table 2). The free sulfonamide is obtained by hydrolysis of the amidine group with aqueous acid.

Compared to the alcohols, the amines generally reacted in a shorter time and gave higher yields (Table 3). Cycloalkylamines (**11a–c**), cyclic amines (**11e–g**) and alkyl amines (**11h–j**) all reacted at room temperature to provide the products in very good yields. Alternate fluoride sources can be used, such as TBAF in dichloromethane, but gave products in slightly lower yields (**11a**,**d** and **j**).

Unlike the sulfonamide ether synthesis, the amines reacted readily under KF/DMSO condition at room temperature with the free sulfonamide **8** to provide the desired amines **12** in good yields (Table 4).

Table 4. 5-Amino substitution products **12**

Entry	NR_3R_4	Base	R_1	R	Yield[a] (%)
12a		KF	F	NH_2	94
12b		KF	F	NH_2	81
12c		KF	F	NH_2	79
12d		KF	F	NH_2	52
12e		KF	F	NH_2	33
12f		KF	F	NH_2	86
12g		KF	F	NH_2	64
12h		KF	H	NH_2	91
12k		KF	H	NH_2	70
12l		KF	H	NH_2	81
12m		KF	H	NH_2	83

[a] Unoptimized yields based on 0.2 mmol scale parallel synthesis.

In summary, the fluoride-mediated substitution of the 5-chloro pyrazoles provides both the 5-amino and ether pyrazoles in a facile manner and is amenable to parallel synthesis.[10,11]

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References and notes

1. (a) Dannhardt, G.; Laufer, S. *Curr. Med. Chem.* **2000**, *7*, 1101–1112; (b) Carty, T. J.; Marfat, A. *Curr. Opin. Anti-Inflamm. Immunomod. Invest. Drugs* **1999**, *1*, 89.
2. Talley, J. J.; Brown, D. L.; Carter, J. S.; Graneto, M. J.; Koboldt, C. M.; Masferrer, J. L.; Perkins, W. E.; Rogers, R. S.; Shaffer, A. F.; Zhang, Y. Y.; Zweifel, B. S.; Seibert, K. *J. Med. Chem.* **2000**, *43*, 775.
3. Li, J.; Lundy DeMello, K. M.; Cheng, H.; Sakya, S. M.; Bronk, B. S.; Rafka, R. J.; Jaynes, B. H.; Ziegler, C. B.; Kilroy, C.; Mann, D. W.; Nimz, E. L.; Lynch, M. P.; Haven, M. L.; Kolosko, N. L.; Minich, M. L.; Li, C.; Dutra, J. K.; Rast, B.; Crossan, R.; Morton, B. J.; Kirk, G. W.; Callaghan, K. M.; Koss, D. A.; Shavnya, A.; Lund, L. A.; Seibel, S. B.; Petras, C. F.; Silvia, A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 95.
4. (a) Leblanc, Y.; Roy, P.; Boyce, S.; Brideau, C.; Chan, C. C.; Charleson, S.; Gordon, R.; Grimm, E.; Guay, J.; Leger, S.; Li, C. S.; Riendeau, D.; Visco, D.; Wang, Z.; Webb, J.; Xu, L. J.; Prasit, P. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2207; (b) Li, C.-S.; Black, W. C.; Brideau, C.; Chan, C. C.; Charleson, S.; Cromlish, W. A.; Claveau, D.; Gauthier, J. Y.; Gordon, R.; Greig, G.; Grimm, E.; Guay, J.; Lau, C. K.; Riendeau, D.; Therien, M.; Visco, D. M.; Wong, E.; Xu, L.; Prasit, P. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3181; (c) Lau, C. K.; Brideau, C.; Chan, C. C.; Charleson, S.; Cromlish, W. A.; Ethier, D.; Gauthier, J. Y.; Gordon, R.; Guay, J.; Kargman, S.; Li, C.-S.; Prasit, P.; Riendeau, D.; Therien, M.; Visco, D. M.; Xu, L. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3187.
5. Sakya, S.; Rast, B. *Tetrahedron Lett.* **2003**, *44*, 7629.
6. (a) Khan, M. A.; Freitas, A. C. C. *J. Heterocycl. Chem.* **1983**, *20*, 277; (b) Bakhite, E. A.; Geies, A. A.; El-Kashef, H. S. *Phosphorus, Sulfur Silicon Relat. Elem.* **2000**, *157*, 107; (c) Molina, P.; Arques, A.; Vinader, M. V.; Becher, J.; Brondum, K. *J. Org. Chem.* **1988**, *53*, 4654; (d) Svenstrup, N.; Simonsen, K. B.; Thorup, N.; Brodersen, J.; Dehaen, W.; Becher, J. *J. Org. Chem.* **1999**, *64*, 2814–2820; (e) Weinges, A.; Balzer, W. R.; Gerstung, S.; Gerstung, S. D. In Ger. *Offen.*; (Wella AG, Germany). De, **1996**, pp 8; (f) Gehring, R.; Schallner, O.; Stetter, J.; Santel, H. J.; Schmidt, R. R. In Ger. *Offen.*; (Bayer A.-G., Fed. Rep. Ger.). De, **1986**, pp 79; (g) Neunhoeffer, H.; Gerstung, S.; Clausen, T.; Balzer, W. In Ger. *Offen.*; (Wella AG, Germany). De, **1994**, pp 14; (h) Dickore, K.; Gehring, R.; Sasse, K.; Santel, H. J.; Schmidt, R. R. In Ger. *Offen.*; (Bayer A.-G., Fed. Rep. Ger.). De, **1986**, pp 88; (i) Park, M.-S.; Park, H.-J.; Park, K. H.; Lee, K.-I. *Synth. Commun.* **2004**, *34*, 1541; (j) *J. Med. Chem.* **1995**, *38*, 3524.
7. (a) L'abbe, G.; Emmers, S.; Dehaen, W.; Dyall, L. K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2553; (b) El-Shekeil, A.; Babaqi, A.; Hassan, M.; Shiba, S. *Acta Chim. Hungarica* **1989**, *126*, 813–820.
8. (a) Clark, J. H. *Chem. Rev.* **1980**, *80*, 429; (b) Sawyer, J. S.; Schmittling, E. A.; Palkowitz, J. A.; Smith, W. J., III. *J. Org. Chem.* **1998**, *63*, 6338.

9. Lee, L. F.; Schleppnik, F. M.; Schneider, R. W.; Campbell, D. H. *J. Heterocycl. Chem.* **1990**, *27*, 243.
10. Sample reaction procedure: 5-Chloro-1-(5-methanesulfonyl-pyridin-2-yl)-3-trifluoromethyl-1*H*-pyrazole-4-carbonitrile (351 mg, 1 mmol) and (4-methylene-cyclohexyl)-methanol (252 mg, 2 mmol) were dissolved in dry dimethylsulfoxide (DMSO) (5 mL) and potassium fluoride (116 mg, 2 mmol) was added to the mixture. The resulting mixture was stirred at 20 °C for a period of 48 h. Analytical HPLC indicated the reaction completion. The reaction mixture was poured into water (15 mL) and the resulting mixture was extracted with ethyl acetate (2×20 mL). The organic extract was dried over magnesium sulfate and concentrated with a rotary evaporator. The desired product **9e** (299 mg, 68%) was isolated by chromatography on silica gel column (Flash 40M; 15% EtOAc:15% acetone in hexane). MS (*m*/*z*): 441 (M+H); retention time (rt): 3.0 min.
11. 5-Chloro-3-difluoromethyl-1-(5-methanesulfonyl-pyridin-2-yl)-1*H*-pyrazole-4-carbonitrile (1.24 g, 3.7 mmol) and 2,6-*cis*-dimethylmorpholine (0.86 g, 7.4 mmol) were dissolved in dry dimethylsulfoxide (DMSO) (13 mL) and potassium fluoride (0.43 g, 7.4 mmol) was added to the clear solution. The resulting mixture was stirred at 20 °C for a period of 2 h. Analytical HPLC indicated the reaction completion. The reaction mixture was poured into water (50 mL) and the resulting mixture was extracted with ethyl acetate (30 mL). The organic extract was dried over sodium sulfate and concentrated with a rotary evaporator. The desired product (1.3 g, 85%) was isolated by triturating the residue with ether (10 mL) containing three drops of methanol, stirring the suspension overnight, filtering and drying under high vacuum. MS (*m*/*z*): 412.5 (M+H); retention time (rt): 2.2 min; ^{1}HNMR: (400 MHz, DMSO-d_6) δ 9.02 (1H, d, $J = 2.4$), 8.52 (1H, dd, $J = 8.8$, 2.8), 7.98 (1H, d, $J = 8.8$), 7.12 (1H, t, $J = 52.8$), 3.68 (2H, m), 3.36 (3H, s), 3.28 (2H, m), 2.80 (2H, m), 0.99 (6H, d, $J = 6.4$) ppm, ^{13}CNMR: (400 MHz, DMSO-d_6) 155.9, 154.2, 148.2, 139.6, 119.2, 113.2, 113.1, 112.0, 109.9, 79.0, 71.6, 55.9, 44.3, 18.9 ppm.