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Facile microwave assisted decarbonylation of 4-formyl group in 5-alkyl amino substituted pyrazoles

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Abstract

Facile decarbonylation of the 4-formyl group in 5-alkyl amino pyrazoles was seen when reacted with catalytic *p*-toluene sulfonic acid in methanol under microwave irradiation to provide parent 4-H pyrazoles in good yields.

Pyrazoles are an important class of compounds used in the pharmaceutical and the agrochemical industry. Drug discovery efforts have led to important pyrazole drugs, such as COX-2 inhibitor celecoxib[1] for treating inflammation and pain and cannabinoid receptor 1 (CB-1) antagonist rimonabant[2] as an anti-obesity agent (Fig. 1). More closely related 5-amino pyrazoles have also been shown to have anti-tumour activity.[3] Our own recent efforts in the search for canine COX-2 selective agents resulted in a potent and selective COX-2 lead (**9**) for canine and feline use (Fig. 1).[4] Towards that effort we developed a synthetic route to prepare 5-alkyl amino and ether substituted pyrazoles using a mild reaction protocol utilizing parallel synthesis to produce a large number of compounds.[5,6] During the synthesis of 5-alkyl amino pyrazoles with 4-nitrile substitution, our attempts to convert the 4-formyl group to an oxime with hydroxyl amine hydrochloride in methanol resulted in a significant decarbonylation side product 4-H pyrazole. Under the oxime forming reaction conditions, we observed decarbonylation in up to 60% yields.[7] We surmised that the decarbonylation was due to the acid present in the reaction condition since the decarbonylation of 4-formyl pyrazoles has been reported intermittently in the literature under thermal and acidic conditions.[8] However, a majority of unsubstituted pyrazoles at the 4-position are generally accessed via decarboxylation methodology.[9] Thus, an alternate facile and mild approach to decarbonylate the 4-formyl group of 5-amino

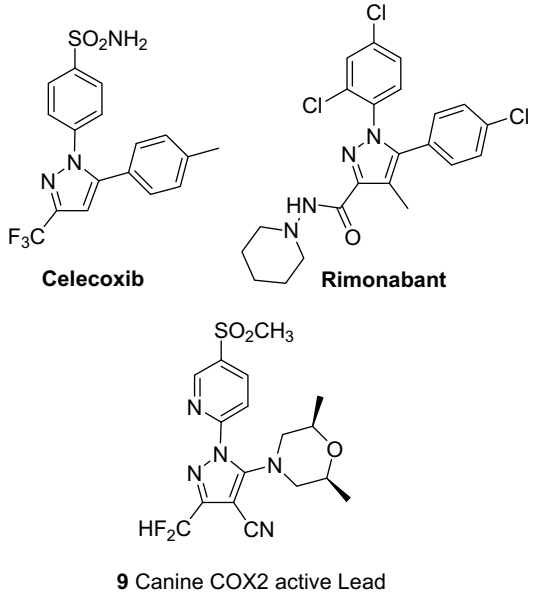

Fig. 1. Lead COX-2 inhibitors and synthetic targets.

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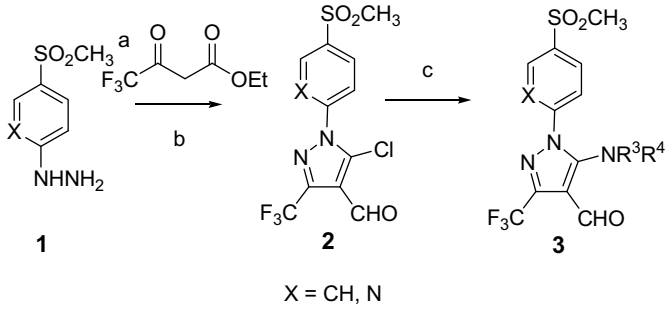
pyrazoles under microwave condition would present a useful alternative.

In our studies, the substitution of the 5-chloro-4-formyl pyrazoles, easily obtained in multigram-scale quantities, provides an ideal way to make 5-amino or ether substituted pyrazoles. The formyl group is generally inert to reaction with both primary and secondary amines and alcohols. With easy access to 5-amino-4-formyl pyrazole precursors, this decarbonylation procedure provides access to 5-alkylamino 4-H (unsubstituted) pyrazole analogs which, based on our own experience,[10] are fairly difficult to access.

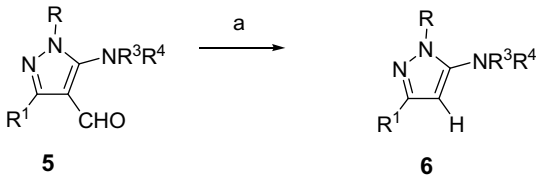
The desired 5-amino 4-formyl pyrazoles **3** were synthesized as shown in Scheme 1 according to our recently reported procedures (See Scheme 2).[4]

The substitution of the chloropyrazoles with amines with either *N*-heteroaryl sulfone, *N*-aryl sulfone or *N*-alkyl groups works quite well (Table 1). The amino substitution yield is low only in the case of cyclobutyl amine substitution of **3n** for reasons that are not quite clear.

Initial studies to decarbonylate the 4-formyl group in **3g** were performed under various acidic conditions. Use of 1 M HCl in dioxane and catalytic *p*-toluene sulfonic acid in refluxing toluene overnight gave the decarbonylated product **6g** in 45% and 89% yields, respectively.[10] However, the use of *p*-TsOH·H_2O in MeOH under microwave irradiation provided the 4-H pyrazoles **6g** in good yields (76%) and in much shorter time (120 °C, 20 min). Expanding this protocol to other amines demonstrated that the pyrazoles undergo decarbonylation with good yields (Table 1).

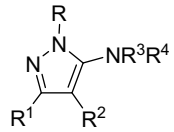


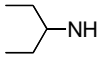
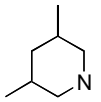
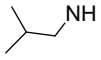
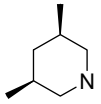
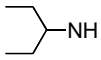
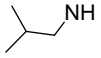
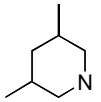
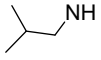
Scheme 1. Reagents and conditions: (a) EtOH, reflux, ~16 h; 2 equiv NaOH, EtOH, 30 min, >80%; (b) $POCl_3$, 4 equiv DMF, 80 °C, 4 h, 60–80%; (c) CsF, R^3R^4NH, DMSO, rt or 80 °C.



Scheme 2. Reagents and conditions: (a) *p*-TsOH·H_2O, MeOH, MW, 120 °C, 20 min.

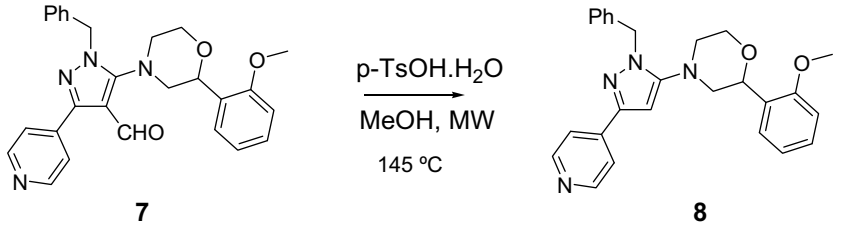
Table 1
Amino pyrazoles **6**



Entry	NR^3R^4	R	R^1	Yield (%) (R^2 = CHO)	Yield[a] (%) (R^2 = H)
3a, 6a		Pyridyl sulfone	CF_3	ND[b]	85.9
3b, 6b		Pyridyl sulfone	CF_3	ND[b]	99.3
3c, 6c		Pyridyl sulfone	CF_3	66.4	66
3d, 6d		Pyridyl sulfone	CF_3	ND[b]	78.4
3e, 6e		Pyridyl sulfone	CF_3	70.9	82.2
3f, 6f		Phenyl sulfone	CF_3	81	83
3g, 6g		Phenyl sulfone	CF_3	54	76.2
3h, 6h		Phenyl sulfone	CF_3	70.4	75.8
3i, 6i		Phenyl sulfone	CF_3	70	69.3
3j, 6j		Phenyl sulfone	CF_3	76.9	82.5
3k, 6k		Methyl	CH_3	78	47
3l, 6l		Phenyl	CH_3	84	60
3m, 6m		Phenyl	CH_3	ND[b]	50
3n, 6n		Phenyl	CH_3	13	80

[a] Isolated yields.
[b] The aldehyde substrate obtained from Pfizer sample bank.

Besides the *N*-heteroaryl sulfone, others such as the *N*-phenyl sulfone (**6f–i**), *N*-phenyl (**6l–n**) and *N*-Me (**6k**) groups are also tolerated. Having both *N*-Me and 3-methyl substitution (**6k**) did however result in lower decarbonylation yield (47%).



Scheme 3. Reagents and conditions: *p*-TsOH·H_2O, MeOH, MW, 145 °C, 45 min.

In an unrelated project, we were required to make 5-amino pyrazoles without substitution at the 4-position as exemplified by compound **8**. Thus the preparation of the intermediate **7** using benzyl hydrazine and pyridyl keto-ester gave 5-chloro-4-formyl pyrazole, which was substituted with 2-methoxyphenyl substituted morpholine in 80% yield. Subjecting pyrazole **7** to catalytic amount of *p*-TsOH·H_2O at 120 °C for 20 min resulted in no reaction, with only starting material recovered. However subjecting the same reaction to 145 °C for 45 min in the microwave showed almost complete reaction (Scheme 3). Additional time under the microwave did not progress the reaction any further. However adding an additional 1 equiv of *p*-TsOH·H_2O and subjecting the resulting mixture to 145 °C for 45 min in the microwave resulted in complete reaction, providing product (**5c**) in 80% isolated yield.[11]

In summary, we have developed a very efficient microwave assisted decarbonylation of 4-formyl pyrazole to provide the parent 4-H pyrazoles. This should be complementary to the standard decarboxylation of acids to make 5-amino substituted pyrazoles.

Acknowledgements

Our sincere thanks to Ms. Jiemin Lu for the synthesis of compound **7** using our previously reported condition. Our thanks also go to Dr. Christopher O'Donnell for his many helpful suggestions to this article.

References and notes

1. Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Doctor, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P. C. *J. Med. Chem.* **1997**, *40*, 1347.
2. Rinaldi-Carmona, M.; Barth, F.; Héaulme, M.; Shire, D.; Calandra, B.; Congy, C.; Martinez, S.; Maruani, J.; Neliat, G.; Caput, D.; Ferrara, P.; Soubrie, P.; Breliere, J. C.; Le Fur, G. *FEBS Lett.* **1994**, *350*, 240.
3. Park, H.-J.; Lee, K.; Park, S.-J.; Ahn, B.; Lee, J.-C.; Cho, H. Y.; Lee, K.-I. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3307.
4. Sakya, S. M.; Demello, K. M. L.; Minich, M. L.; Rast, B.; Shavnya, A.; Rafka, R. J.; Koss, D. A.; Cheng, H.; Li, J.; Jaynes, B. H.; Ziegler, C. B.; Mann, D. W.; Petras, C. F.; Seibel, S. B.; Silvia, A. M.; George, D. M.; Lund, L. A.; St. Denis, S.; Haven, M. L.; Lynch, M. P. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 288.
5. Sakya, S. M.; Rast, B. *Tetrahedron Lett.* **2003**, *44*, 7629.
6. Shavnya, A.; Sakya, S. M.; Minich, M. L.; DeMello, K. L.; Jaynes, B. H. *Tetrahedron Lett.* **2005**, *46*, 6887.
7. Sakya, S. M.; Hou, X.; Minich, M. L.; Rast, B.; Shavnya, A.; Demello, K. M. L.; Cheng, H.; Li, J.; Jaynes, B. H.; Mann, D. W.; Petras, C. F.; Seibel, S. B.; Haven, M. L. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1067.
8. (a) Ohsawa, A.; Wada, I.; Igeta, H. *Chem. Pharm. Bull.* **1986**, *34*, 1023; (b) Eltsov, O. S.; D'yachenko, E. V.; Glukhareva, T. V.; Morzherin, Y. Y. *Mendeleev Commun.* **2005**, 119; (c) El-Shekeil, A.; Babaqi, A.; Hassan, M.; Shiba, S. *Acta Chim. Hungarica* **1989**, *126*, 813.
9. (a) Guerrini, G.; Costanzo, A.; Ciciani, G.; Bruni, F.; Selleri, S.; Costagli, C.; Besnard, F.; Costa, B.; Martini, C.; De Siena, G.; Malmberg-Aiello, P. *Bioorg. Med. Chem.* **2006**, *14*, 758; (b) Meegalla, S. K.; Doller, D.; Sha, D.; Soll, R.; Wisnewski, N.; Silver, G. M.; Dhanoa, D. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4949; (c) Bondavalli, F.; Botta, M.; Bruno, O.; Ciacci, A.; Corelli, F.; Fossa, P.; Lucacchini, A.; Manetti, F.; Martini, C.; Menozzi, G.; Mosti, L.; Ranise, A.; Schenone, S.; Tafi, A.; Trincavelli, M. L. *J. Med. Chem.* **2002**, *45*, 4875; (d) Seneci, P.; Nicola, M.; Inglesi, M.; Vanotti, E.; Resnati, G. *Synth. Commun.* **1999**, *29*, 311; (e) Frigola, J.; Colombo, A.; Pares, J.; Martinez, L.; Sagarra, R.; Roser, R. *Eur. J. Med. Chem.* **1989**, *24*, 435.
10. Unpublished results of initial efforts.
11. *General sample decarbonylation procedure*: A mixture of **3b** (50.9 mg, 0.131 mmol) and *p*-TsOH·H_2O (0.2 equiv, 5.0 mg, 0.026 mmol) in methanol (1 ml) was microwaved to 120 °C for 20 min. The reaction mixture was concentrated and purified by preparative TLC (Whatman 1000 μm plate) with 20% EtOAc/hexane as eluant to give the desired pyrazole **6d** (46.9 mg, 99.3% yield) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 8.28 (d, 1H, $J = 8.7$ Hz), 8.18 (d, 1H, $J = 8.7$ Hz), 7.94 (br s, 1H, NH), 5.56 (s, 1H, 4-H), 3.87 (p, 1H, $J = 7.9$ Hz, NCH), 3.13 (s, 3H, CH_3), 2.50 (m, 2H, CH_2), 2.02 (m, 2H, CH_2), 1.84 (m, 2H, CH_2); MS (*m*/*z*) 361.2 (M+H).