

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.

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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 celecoxib¹ for treating inflammation and pain and cannabinoid receptor 1 (CB-1) antagonist rimonabant² 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 intermit-

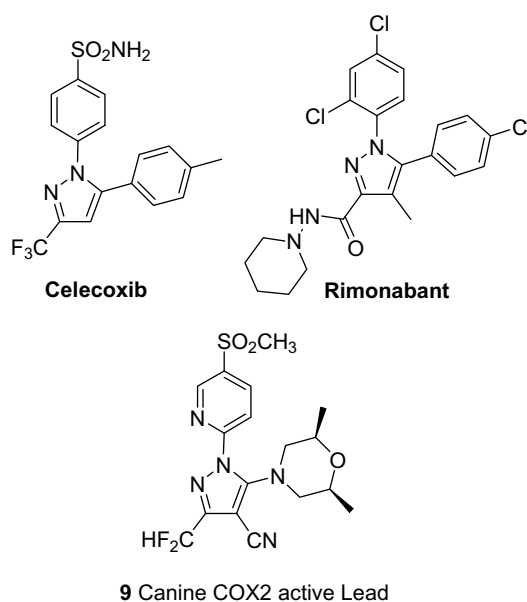


Fig. 1. Lead COX-2 inhibitors and synthetic targets.

tently 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

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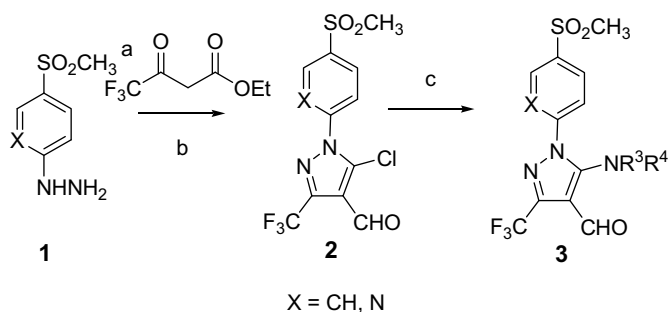
pyrazoles under microwave condition would present a useful alternative.

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-alkyl-amino 4-H (unsubstituted) pyrazole analogs which, based on our own experience,¹⁰ are fairly difficult to access.

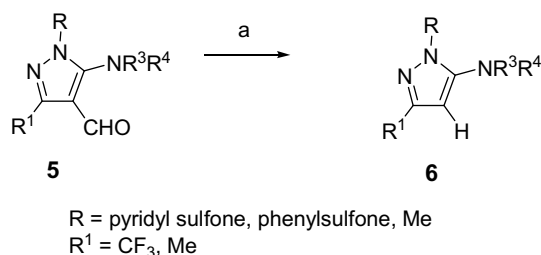
The desired 5-amino 4-formyl pyrazoles **3** were synthesized as shown in Scheme 1 according to our recently reported procedures (See Scheme 2).⁴

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·H₂O 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).

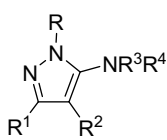


Scheme 1. Reagents and conditions: (a) EtOH, reflux, ~16 h; 2 equiv NaOH, EtOH, 30 min, >80%; (b) POCl₃, 4 equiv DMF, 80 °C, 4 h, 60–80%; (c) CsF, R³R⁴NH, DMSO, rt or 80 °C.



Scheme 2. Reagents and conditions: (a) *p*-TsOH·H₂O, MeOH, MW, 120 °C, 20 min.

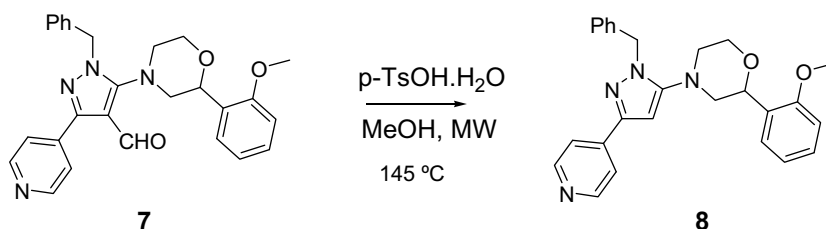
Table 1
Amino pyrazoles **6**

					
Entry	NR ³ R 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·H₂O, 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·H₂O 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·H₂O 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

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- Unpublished results of initial efforts.
- General sample decarbonylation procedure:** A mixture of **3b** (50.9 mg, 0.131 mmol) and *p*-TsOH·H₂O (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. ¹H NMR (400 MHz, CDCl₃) 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, CH₃), 2.50 (m, 2H, CH₂), 2.02 (m, 2H, CH₂), 1.84 (m, 2H, CH₂); MS (*m/z*) 361.2 (M+H).