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Studies towards the synthesis of Fipronil® analogues: improved decarboxylation of α-hydrazonoacid derivatives

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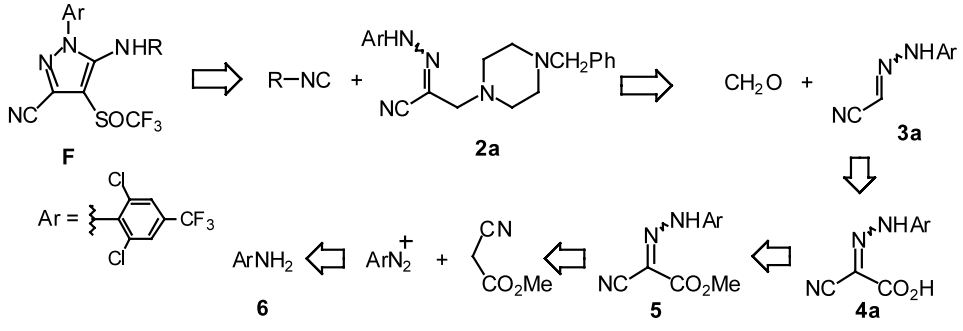
Abstract—The Mannich reaction of hydrazones coupled with a [4+1] cycloaddition with isocyanides has been used for the synthesis of aminopyrazole analogues of Fipronil®. The starting cyanohydrazone was prepared with new experimental conditions for efficient diazonium coupling in fluorinated solvents followed by a new sodium cyanide catalysed decarboxylation. © 2002 Published by Elsevier Science Ltd.

Fipronil® **F** (Scheme 1, R = H) is a new fluorinated pyrazole with high insecticide activity;[1] in the search for new methods for the synthesis of Fipronil® analogues, we were interested in evaluating the use of the Mannich/[4+1] cycloaddition reactions of hydrazones recently disclosed in our research group.[2,3] The starting cyanohydrazone **3a** could be obtained by diazotation of aniline **6** followed by coupling with methylcyanoacetate, saponification and decarboxylation (Scheme 1). Unexpected problems using this approach eventually led us to define original conditions for the diazonium coupling with methylcyanoacetate as well as a new catalysed decarboxylation of α-hydrazonoacids.

Diazotation of electronwithdrawing group substituted anilines often requires the use of large excess of acid to prevent the triazene formation associated with incomplete protonation of the aniline. Optimal one pot diazotation–diazonium coupling of aniline **6** was obtained with *t*-butyl nitrite in a mixture of trifluoroacetic acid and trifluoroethanol (3/2) as solvent, followed by addition of methyl cyanoacetate and neutralisation with potassium hydroxide (as a 1/1 concentrated solution in water). The cyanohydrazone **5** was thus obtained in a 83% isolated yield (Scheme 2). The choice of this complex solvent system was dictated by the need of a large excess of acid for the diazotation process without any solidification of the mixture during the diazonium coupling in basic medium. Saponification of ester **5** in 2N aqueous NaOH led to the corresponding acid **4a** in good yields (Scheme 2).

Attempted thermal decarboxylation of cyanohydrazonoacid **4a** as described for *N*-phenylcyanohydrazone failed to give any isolated product.[4] The decarboxylation of electronwithdrawing group substituted arylcyanohydrazonoacids is known to be difficult due to competing formation of dicyanogen with elimination of



Scheme 1.

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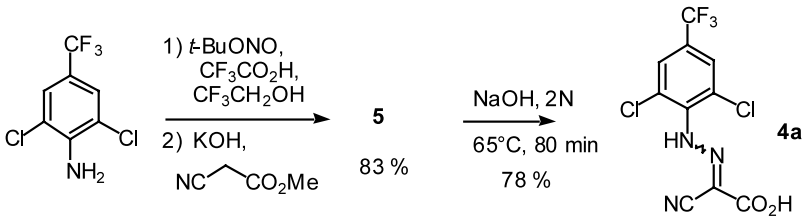
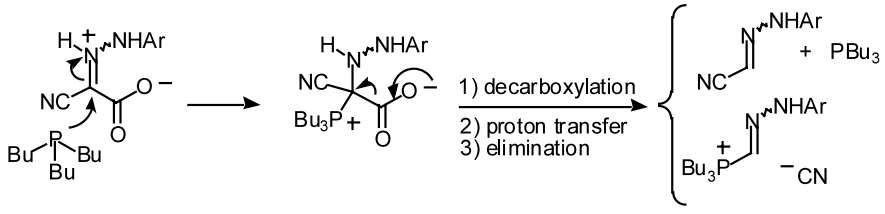


Scheme 2.

substituted anilines.[4] The catalytic effect of tributylphosphine for the room temperature decarboxylation of various α-imino and α-hydrazono acids has been described by Barton et al.;[5] under these conditions, the decarboxylated hydrazone **3a** was obtained in a moderate 48% isolated yield. As suggested by Barton et al, a possible mechanism implies the addition–elimination of the phosphine on the hydrazone to allow the decarboxylation on a quaternary center. In our case, the leaving group properties of the cyano substituent may alter the catalytic cycle involving the phosphine (Scheme 3).

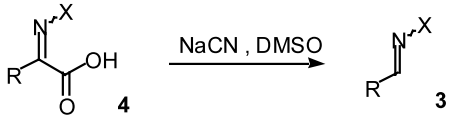
We postulate that cyanide anion could compete efficiently with tributylphosphine as a catalyst in this reaction, offering furthermore the advantage of degenerative pathways in the various possible cyanide eliminations. Indeed when hydrazone **4a** was treated with sodium cyanide in DMSO at room temperature, the decarboxylated hydrazone **3a** was now obtained in a 62% isolated yield (Table 1). As shown by the examples described in Table 1, the interest of this procedure is not restricted to cyano substituted hydrazones as phenylglyoxylic acid hydrazone **4c** was equally decarboxylated under cyanide catalysis. The behaviour of oximes **4e** is close to the one of hydrazone **4c**; with less electronwithrawing groups tethered on the hydrazone, heating is required for the decarboxylation to proceed.

With this improved decarboxylation reaction in hand, we were very pleased to observe efficient Mannich coupling with formation of **2a** without any competing elimination of the cyanide under piperazine treatment (Scheme 4). Alternatively, the dimethylamino substi-

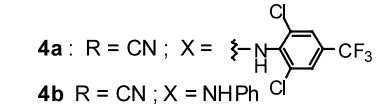


Scheme 3.

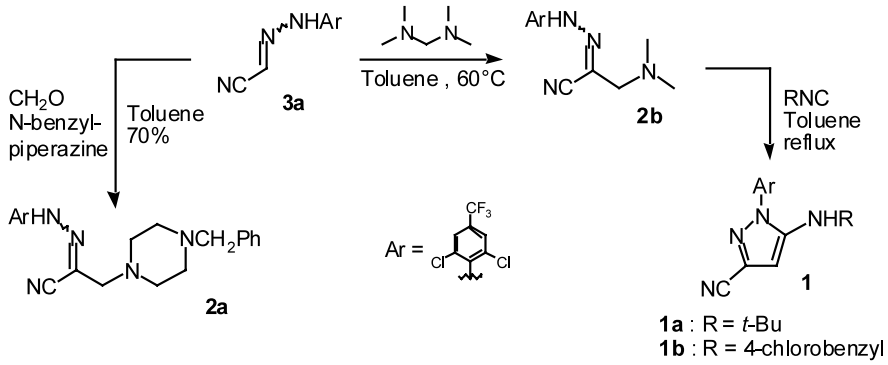
Table 1. Decarboxylation of α-hydrazono and α-oximinoacids



Entry	Starting **1**	Catalyst	Temperature	Time (h)	Yield (%)[a]
1	**4a**	NaCN	rt	0.5	62
2	**4a**	PBu_3	rt	3	48
3	**4b**	NaCN	rt	0.5	60
4	**4b**	PBu_3	rt	3	45
5	**4c**	NaCN	65°C	12	50
6	**4c**	PBu_3	65°C	12	30
7	**4d**	NaCN	rt	0.5	70
8	**4e**	NaCN	65°C	1	45



[a] To a solution of acid **4** (1 mmol) in DMSO (3 ml) was added sodium cyanide (1 mmol) and the mixture stirred for the time and temperature shown in Table 1. Comparative reactions with tributylphosphine were performed with 0.5 equiv. phosphine in the same conditions.



Scheme 4.

tuted hydrazone **2b** could be obtained in a 90% isolated yield by treatment with tetramethyldiaminomethane. The aminohydrazone **2b** was then easily converted to aminopyrazoles **1** by a [4+1] cycloaddition reaction with isocyanides. The azoalkene precursor was obtained in this case by a mere thermal treatment in toluene and trapped in situ by *t*-butylisocyanide or 4-chlorobenzylisocyanide to give the expected pyrazoles **1a** and **1b** in a 50 and 52% isolated yield respectively (Scheme 4).

In conclusion, we have disclosed an expedient access to *N*-substituted analogues of Fipronil® from cyanohydrazone **3a**. This was made possible by the new experimental conditions defined for the diazonium coupling and the decarboxylation reaction to prepare **3a**. The interest and scope of these procedures will be studied further.

Acknowledgements

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