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Mannich reaction of trifluoroacetaldehyde hydrazones, a useful entry to trifluoromethyl substituted heterocycles.

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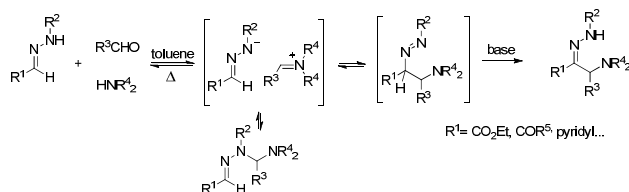
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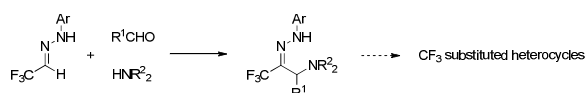
NH-aryl hydrazones derived from trifluoroacetaldehyde hemiacetal may be involved in efficient Mannich type reaction with formaldehyde and aromatic aldehydes. The resulting hydrazones are useful building blocks for the preparation of trifluoromethyl substituted heterocycles as shown by a straightforward preparation of 1,2-diazine derivatives under heating with β -ketoesters.

Since the first Mannich couplings and the demonstration of its power in total synthesis by Robinson,¹ this reaction has never ceased to attract the attention of chemists who proposed over the years many extensions working both on the nature of the nucleophiles and the stereoselectivity of the processes.² The Mannich reaction of N-H hydrazones has been first proposed by Keil and Ried in 1959.³ The reaction was only described with formaldehydes and rather acidic hydrazones prone to easy deprotonation under the condition of the reaction.⁴ In opposition to usual behavior of hydrazone anions in alkylations, reversible attacks on nitrogen leads to exclusive functionalisation at the C-position of the hydrazone (Scheme 1).

Mannich reaction of NH-hydrazones:^{3,4}



This work: Mannich reaction of NH-trifluorohydrazones:



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Scheme 1. Mannich couplings of NH-hydrazones.

A base triggered irreversible azo-hydrazone tautomerism is required for the efficiency of the process. This explains the need for an electronwithdrawing ketone, ester or pyridyl moieties tethered at the α -position of the hydrazone in order to raise the acidity of the azo intermediate.⁵ Considering these limitations we envisioned that an NH-hydrazone derived from trifluoroacetaldehyde may be sufficiently acidic to be involved in efficient Mannich type couplings leading in turn to valuable trifluoromethylated heterocycles (Scheme 1). Herein, we wish to present our results in this direction.

Apart from some oxidative/cycloaddition cascades⁶ as well as several Michael additions with α,β -unsaturated aldehydes,⁷ the reactivity of NH-trifluoromethyl hydrazones has been poorly studied. These hydrazones are easily obtained under heating trifluoroacetaldehyde hemiacetals and hydrazines in water solution, in the presence of hydrochloric acid.⁸ 4-nitrophenyl hydrazone **1a**, obtained in 90% yield from 4-nitrophenyl hydrazine, was initially selected due to its higher acidity and the reported beneficial effect of a nitro substituent in Mannich coupling of non fluorinated NH-Arylhydrazones.⁵ When **1a** was added to morpholine and 4-chlorobenzaldehyde under conditions optimized for non fluorinated hydrazones (equimolar amounts in refluxing toluene),^{4a,b} we were delighted to observe a quantitative formation of the new Mannich fluorinated adduct **4a** after refluxing the mixture for 12 hours (Table 1). To evaluate the potential of this coupling different N-Aryl fluorinated hydrazones **1** were prepared and treated together with morpholine and various aldehydes (Table 1). Using nitrosubstituted hydrazone **1a**, the reaction does seem to show a strong dependence to the electronic nature of the aromatic aldehyde, electron-rich and deficient aromatic aldehydes giving both very good yields (Table 1, entries 4, 5, 7, 8). Heteroaromatic aldehydes may be used as well giving lower yields for electron-rich derivatives (indole, thiophene versus pyridine, Table 1, entries 9, 10, 11). 2-substituents are not

tolerated on the aromatic ring as shown by the lack of any coupling observed with 2-nitro and 2-methoxy benzaldehydes (Table 1, entries 3, 6). In strong contrast with its non fluorinated hydrazone analogue, the reaction could not be extended to the coupling of simple aliphatic aldehydes such as acetaldehyde or isovaleraldehyde (Table 1, entries 13, 14). However, the more reactive formaldehyde and trifluoroacetaldehyde (used as its hemiacetal) could give some productive couplings (Table 1, entries 1, 12, 15, 17, 19, 24). Rewardingly, the reaction was not limited to nitrophenylhydrazone **1a**. Indeed simple N-phenyl or N-tolyl trifluoromethylhydrazones afforded Mannich adducts with similar yields compared to their nitro analogue. When comparing the lack of reactivity of the related N-phenyl acetaldehyde hydrazone in Mannich reactions, this behavior clearly demonstrates a strong activating effect the trifluoromethyl group. Beside morpholine, the coupling could be also easily extended to other cyclic and non cyclic secondary amines (Table 1, entries 21-26).

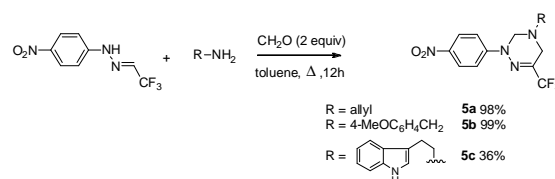
Table 1. Mannich reaction of fluorinated **1** using morpholine

entry	1	2	3a	3	4	Yield(%) ^a
1	4-NO ₂ C ₆ H ₄	H	morpholine	morpholine	4a	(94)
2	4-NO ₂ C ₆ H ₄	4-ClC ₆ H ₄	morpholine	morpholine	4b	(99)
3	4-NO ₂ C ₆ H ₄	2-NO ₂ C ₆ H ₄	morpholine	morpholine	-	-
4	4-NO ₂ C ₆ H ₄	3-NO ₂ C ₆ H ₄	morpholine	morpholine	4c	(99)
5	4-NO ₂ C ₆ H ₄	4-NO ₂ C ₆ H ₄	morpholine	morpholine	4d	(99)
6	4-NO ₂ C ₆ H ₄	2-MeOC ₆ H ₄	morpholine	morpholine	-	-
7	4-NO ₂ C ₆ H ₄	3-MeOC ₆ H ₄	morpholine	morpholine	4e	(99)
8	4-NO ₂ C ₆ H ₄	4-MeOC ₆ H ₄	morpholine	morpholine	4f	(82)
9	4-NO ₂ C ₆ H ₄	2-thiophenyl	morpholine	morpholine	4g	(48)
10	4-NO ₂ C ₆ H ₄	3-pyridyl	morpholine	morpholine	4h	(99)
11	4-NO ₂ C ₆ H ₄	N-Methyl-3-indolyl	morpholine	morpholine	4i	(58)
12	4-NO ₂ C ₆ H ₄	CF ₃ ^b	morpholine	morpholine	4j	(79)
13	4-NO ₂ C ₆ H ₄	Me	morpholine	morpholine	-	-
14	4-NO ₂ C ₆ H ₄	<i>iso</i> -butyl	morpholine	morpholine	-	-
15	Ph	H	morpholine	morpholine	4k	(95)
16	Ph	4-ClC ₆ H ₄	morpholine	morpholine	4l	(85)
17	4-MeC ₆ H ₄	H	morpholine	morpholine	4m	(95)
18	4-MeC ₆ H ₄	4-ClC ₆ H ₄	morpholine	morpholine	4n	(68)
19	2-pyridyl	H	morpholine	morpholine	4o	(81)
20	2-pyridyl	4-ClC ₆ H ₄	morpholine	morpholine	4p	(47)
21	4-NO ₂ C ₆ H ₄	4-ClC ₆ H ₄	pyrrolidine	pyrrolidine	4q	(82)
22	4-NO ₂ C ₆ H ₄	4-ClC ₆ H ₄	piperidine	piperidine	4r	(87)
23	4-NO ₂ C ₆ H ₄	4-ClC ₆ H ₄	N-benzyl-piperazine	N-benzyl-piperazine	4s	(81)
24	4-NO ₂ C ₆ H ₄	H	diethylamine	diethylamine	4t	(89)
25	Ph	4-ClC ₆ H ₄	piperidine	piperidine	4u	(75)
26	2-pyridyl	4-ClC ₆ H ₄	pyrrolidine	pyrrolidine	4v	(58)

^a) isolated yields after column chromatography on silica gel. ^b) ethyl trifluoroacetaldehyde hemiacetal was used

In a context of growing medicinal interest for new fluorinated compounds and trifluoromethylated compounds in particular, this reaction offers interesting opportunities for the

preparation of new trifluoromethylated heterocycles.⁹ A first family of trifluorinated 1,2,4-triazines **5** could be easily obtained when primary amines such as allylamine or 4-methoxybenzylamine were reacted with hydrazone **1a** and a two fold excess of formaldehyde (Scheme 2).¹⁰



Scheme 2. 1,2,4-Triazines formation from NH-hydrazones

More interestingly, aminohydrazones such as **4a** represent potential starting materials for the generation of reactive fluorinated azoalkenes. When substituted by electron-withdrawing groups (esters, ketones tethered on N or carbon atoms), azoalkenes have been widely described as efficient Michael acceptors as well as good partners in hetero Diels-Alder reactions.¹¹ Azoalkenes are usually obtained under basic treatment of NH-chlorohydrazones,¹² they may be also prepared under simple thermal elimination of amine from hydrazonoamines.¹³ Elimination of amines from Mannich-type adducts of hydrazones are usually observed for amine partners with rather low boiling point in order to limit the reverse Michael addition. Knowing that β -Ketoesters additions to azoalkenes substituted by electronwithdrawing groups are known to afford pyrroles or 1,2-diazines according to the nature and position of the electron-withdrawing groups,¹⁴ we were interested to examine whether the trifluoromethyl group might be activating enough to allow a Michael/cyclization cascade. Thus, we decided to react directly the morpholino Mannich adducts **4a** with acetylacetone used as solvent. The temperature was fixed at 130 °C, hoping that the Mannich-azoalkene equilibrium could be shifted by the formation of an intermediate enamine between the morpholine and the diketone.¹⁵ Rewardingly heating **4a** in acetylacetone (0.17 M) at 130 °C for 12 hours afforded 4-hydropyridazine **7a** in 58 % isolated yields (Table 2, entry 1).

Table 2. 4-hydropyridazine **7** from Mannich adducts **4**

entry	4	6	7	Yield(%) ^a
1	4a	6a	7a	58
2	4b	6b	7b	34 ^b
3	4b	6a	7c	80
4	4i	6a	7d	92
5	4l	6c	7e	90
6	4p	6a	7f	56
7	4m	6a	7g	77
8	4l	6a	7h	71
9	4l	6d	7i	68

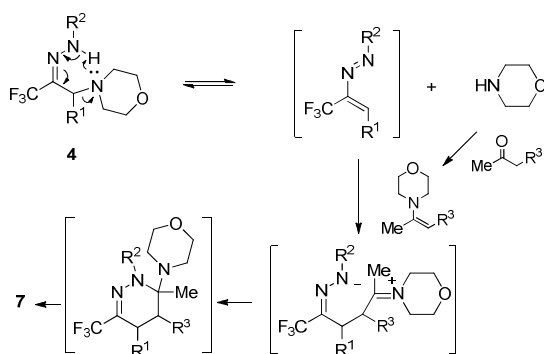
$\begin{matrix} R^1 = H, R^2 = H \\ R^1 = H, R^2 = H \\ R^1 = H, R^2 = CO_2Me \\ R^1 = H, R^2 = (CH_2)_3 \\ R^1 = H, R^2 = (CH_2)_2 \end{matrix}$

 $\begin{matrix} R^3 = H, R^4 = COMe \\ R^3 = H, R^4 = H \\ R^3 = H, R^4 = CO_2Me \\ R^3 = H, R^4 = (CH_2)_3 \\ R^3 = H, R^4 = (CH_2)_2 \end{matrix}$

10 4l 6e 7j 90

a) isolated yields after column chromatography on silica gel. b) the reaction was performed under microwave conditions at 130 °C for one hour.

Several Mannich adducts **4** were then treated with ketones **6** under the same conditions leading to diazines **7** in moderate to excellent yields (Table 2, entries 2-10). The reaction does not seem to depend much on the nature of the starting arylhydrazines as shown by the good yields obtained using nitrophenyl (Table 2, entries 1-4), phenyl (Table 2, entries 5, 8-10) or pyridyl (Table 2, entry 6) substituents. The formation of **7b** in a low 34% yields may be probably explained by the required shorter reaction time associated with the use of microwave conditions. The examples obtained with cyclopentanone and cyclohexanone (Table 2, entries 9,10) are indicative of the efficiency of the process and further support our initial mechanistic hypotheses: thermal elimination of morpholine allows the formation of an intermediate enamine which is engaged in a Michael addition with the azoalkene. Cyclization and elimination of morpholine finally afford **7** (Scheme 3).



Scheme 3. Possible mechanism for the formation of **7** from **4**.

Conclusions

The present study demonstrates the interest of trifluoroacetaldehyde NH-Aryl hydrazone as carbon centered nucleophiles in Mannich reactions. The electron-withdrawing properties of the trifluoromethyl group are strongly associated with the success of the couplings allowing various NH-Aryl hydrazone derivatives to react with formaldehyde as well as different aromatic aldehydes. The resulting Mannich adducts are valuable starting materials for the generation of azoalkene intermediates and the preparation of trifluoromethyl substituted heterocycles.

Acknowledgements

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Conflicts of interest

There are no conflicts to declare.

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