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Chiral *trans*-carboxylic trifluoromethyl 2-imidazolines by a Ag_2O-catalyzed Mannich-type reaction

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ABSTRACT

Trifluoromethyl aldimines derived from α-amino esters have proven to be very good starting materials to obtain the title compounds. A Ag_2O-catalyzed Mannich-type/cyclization cascade reaction starting from suitable α-isocyano acetates leads to enantiopure valuable *trans*-carboxylic trifluoromethyl substituted 2-imidazolines by a highly stereoselective addition without the need to add organocatalysts.

1. Introduction

2-Imidazolines are an important class of heterocyclic compounds due to their wide applications in different chemistry fields. They can be found in natural product chemistry, pharmaceutical chemistry, organic synthesis, coordination chemistry, and homogeneous catalysis.[1] Furthermore, carboxylic substituted 2-imidazolines are cyclic analogues of α,β-diamino acids,[2] key structural units of several natural products, having great relevance in the synthesis of bioactive compound derivatives characterized by exclusive pharmacological profiles. α,β-Diamino acids have also been used to induce specific conformations in peptide segments, or as precursors of imidazoline derivatives with therapeutic activity, increasing the resistance to hydrolysis.[3]

Many new efficient methods to synthesize 2-imidazolines as well as modifications of traditional methods have been reported. Among these, a remarkable example is the reaction between imines and both unactivated or activated isocyanides[4] to give racemic 2-imidazolines. In addition, starting from α-isocyano acetates,[5] carboxylic substituted 2-imidazolines can be obtained. These Mannich-type/cyclization cascade reactions are usually base[5g] or metal catalyzed, but the simultaneous use of both have also been reported.[6]

In particular, the development of transition metal-catalyzed processes provides access to both *cis* or *trans* isomers, under mild conditions and starting from the same materials.[1,7] Moreover, since the first asymmetric form of this reaction was reported,[4] a variety of enantioselective approaches have been widely investigated.[5] The structural diversity introduced on the imidazoline ring are many, but only one example of a CF_3-substituted 2-imidazoline is reported,[8] despite the relevance of the trifluoromethyl group on the molecular behaviour.[9] As is well known, the incorporation of fluorine-containing groups into an organic molecule often drastically perturbs the chemical, physical, and biological properties of the parent compound.[10]

Given the broad utility of trifluoromethyl heterocycle compounds in medicinal chemistry,[11] our attention was directed towards the synthesis of carboxylic trifluoromethyl-substituted 2-imidazolines (Scheme 1) by a Mannich-type addition/cyclization cascade reaction between trifluoromethyl aldimines[12] and suitable α-isocyano acetates.[13]

2. Results and discussion

First, the addition was tested by reaction of an equimolar mixture of trifluoromethyl aldimine **1a** and methyl 2-isocyanoacetate (**2**) in THF at rt without catalyst,[14] but no reaction occurred and both reagents were quantitatively recovered (48 h). Even when changing the reaction conditions (solvent, temperature, molar ratios), no addition product was observed. Then, a

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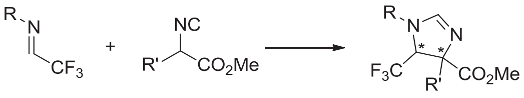
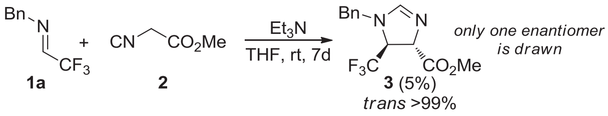


Scheme 1. Synthesis of carboxylic trifluoromethyl substituted 2-imidazolines.



Scheme 2. Base-promoted Mannich-type reaction.

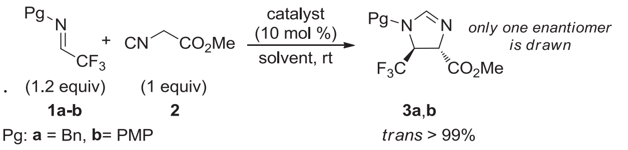
base-promoted Mannich-type reaction was attempted and several tertiary amines (Et_3N, DBU, DMAP, DABCO) have been examined. Only performing the reaction in THF using a stoichiometric amount of Et_3N, 2-imidazoline *trans*-**3**[7b,15] was obtained, although in long reaction times and low yields (Scheme 2).

Next, we focused our attention on a metal-catalyzed addition/cyclization cascade reaction. Given our success in the $ZrCl_4$-catalyzed additions of nucleophiles to trifluoromethyl aldimines,[16] zirconium tetrachloride was considered as a suitable Lewis acid, also because it is easy to handle, cheap and environmentally friendly.[17] However, its catalytic use at room temperature failed in the reaction between α-isocyano acetate **2** and aldimine **1a** and only a complex crude mixture was recovered, even working at lower temperature (0 °C). Furthermore, other different Lewis acids such as $CuCl_2$, Cu_2O and $ZnCl_2$ were tested by us under different conditions, but with no results in any case.

Finally, we envisioned the catalytic activity of silver(I) derivatives, considering their efficiency in the 2-imidazoline formation.[5a-e,14c] Working in THF at room temperature, Ag_2O (10 mol %) provided the best result, affording the desired product *trans*-**3a** in higher yield and in shorter reaction time (Table 1, entry 3).

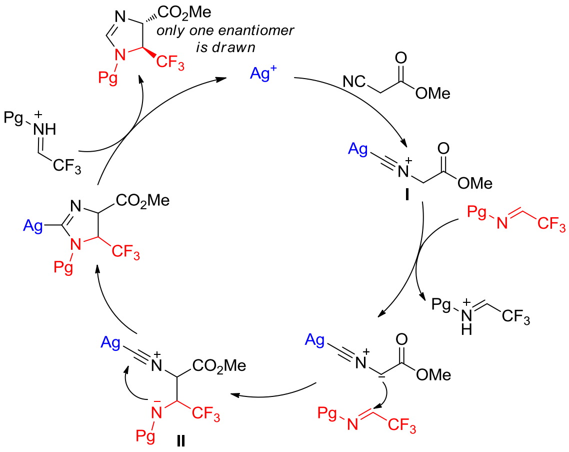
Further examination of the solvent effect, ranging from aprotic polar (entries 4–7) to protic polar (entries 5–9), revealed that the performance of the silver oxide-catalyzed addition does not seem to be influenced by the solvent; we observed a slight decrease of the yield only by using EtOH or iPrOH. The best result was achieved working under solvent-free conditions (entry 10) and *trans*-**3a** was successfully obtained within 5 h (*vs* 15 h, entries 5–7) with higher yield and purity. Varying the aldimine *N*-protecting group and working under the same solvent-free conditions of entry 10, the expected *trans*-2-imidazoline **3b** was found in good yield (entry 11).

Table 1
Optimization of the addition/cyclization cascade reaction of **2** on achiral trifluoromethyl aldimines.



Entry	Pg	3	Catalyst	Solvent	Time (h)	Yield[a] (%)
1	Bn	**a**	AgOAc	THF	22	46
2	Bn	**a**	$AgNO_3$	THF	24	52
3	Bn	**a**	Ag_2O	THF	18	60
4	Bn	**a**	Ag_2O	CH_2Cl_2	20	62
5	Bn	**a**	Ag_2O	DMSO	15	66
6	Bn	**a**	Ag_2O	NMP	15	63
7	Bn	**a**	Ag_2O	DMF	15	65
8	Bn	**a**	Ag_2O	EtOH	16	45
9	Bn	**a**	Ag_2O	iPrOH	15	40
10	Bn	**a**	Ag_2O	–	5	85
11[b]	PMP	**b**	Ag_2O	–	5	88

[a] After flash chromatography on silica gel.
[b] No reaction occurred without catalyst.



Scheme 3. Proposed mechanism for the silver(I)-catalyzed Mannich-type addition/cyclization cascade reaction.

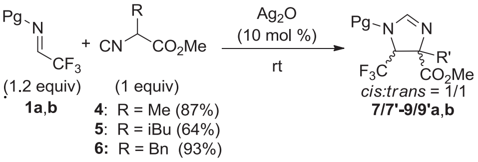
On the basis of the collected results and supported by the data reported in the literature,[13,14a,b,18] a mechanism for the silver(I)-catalyzed Mannich-type reaction is depicted in Scheme 3.

After deprotonation of the activated isocyanide **I**, the formed enolate leads to **II**. The ring closure reaction followed by silver(I) cation/proton exchange provides the *trans*-2-imidazoline, as has been widely reported for the analogous reaction on unfluorinated aldimines.[4b,c,f,5c,g,f]

Next, three different α-substituted isocyano acetates **4**–**6** were synthesized starting from α-amino acid methyl ester hydrochlorides, through slight modifications of the standard protocol,[14a,19] and then tested in the reaction with **1a**,**b** and aldimine **1c** derived from β-alanine (Table 2).

While the reactions involving **4** proceeded as expected under solvent-free conditions (entries 1–2), starting from **5** or **6** the use of CH_2Cl_2 was specifically required to afford the desired products (entries 3–6).[20] The data reported in Table 2 seems to show that the presence of a steric hindrance on the pronucleophile carbon only partially influence the reaction yields, but significantly controls the reaction diastereoselectivity.[21] Actually, the substituent on the nucleophile carbon could be responsible for the similar energy

Table 2
Silver(I)-catalyzed Mannich-type reactions of α-isocyano methyl esters **4**–**6** to achiral aldimines.



Entry	R	R′	Product	Solvent	Time (h)	Yield[a] (%)
1	Bn	Me	**7/7′a**	–	4	60
2	PMP		**7/7′b**	–	4	58
3	Bn	iBu	**8/8′a**	CH_2Cl_2	16	54
4	PMP		**8/8′b**	CH_2Cl_2	16	56
5	Bn	Bn	**9/9′a**	CH_2Cl_2	12	48
6	PMP		**9/9′b**	CH_2Cl_2	10	50

[a] After flash chromatography on silica gel.