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COMMUNICATION

Silver-Catalyzed Formal [3+2]-Cycloaddition of α-Trifluoromethylated Methyl Isocyanides: Facile Stereoselective Synthesis of CF₃-Substituted Heterocycles[†]

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A Ag-catalyzed formal [3+2]-cycloaddition of α trifluoromethylated methyl isocyanides with polar double bonds has been developed for the facile access to trifluoromethylated oxazolines, imidazoline and pyrroline 10 under mild conditions. The practicality of this chemistry is demonstrated by an excellent-yielding, gram-scale synthesis, and facile transformations of the formed oxazolines to trifluoromethylated β -amino alcohols in quantitative yields.

Because incorporation of fluorine atoms or fluoroalkylated ¹⁵ groups into organic molecules often leads to dramatic changes in their chemical, physical and biological properties, trifluoromethylated heterocycles play a significant role in the pharmaceutical chemistry, agrochemistry, and material science.¹ While a number of synthetic methods for the construction of CF₃-²⁰ substituted heterocycles relying on the direct trifluoromethylation of heterocycles² or the cyclization of CF₃-containing building blocks³ have been reported, the development of facile and practical synthetic approaches is still of great interest.

Since it was exploited by Schöllkopf and Gerhart in 1968,⁴ ²⁵ active methylene isocyanides have found wide applications in organic synthesis.⁴⁻⁹ A number of electron-withdrawing groups (EWG) substituted methyl isocyanides have been prepared as valuable synthons,⁵⁻¹⁰ such as isocyanoacetate,⁶ tosylmethyl isocyanide (TosMIC),⁷ isocyanoacetamide,⁸ isocyanoacetonitrile⁹ ³⁰ and isocyanomethylphosphonate¹⁰ (Figure 1). Among them, isocyanoacetate,⁶ TosMIC⁷ and isocyanoacetamide⁸ are notable examples and have been shown to participate in various types of transformations for the synthesis of diverse class of nitrogen containing heterocycles and amino acid derivatives. In principle, ³⁵ the strong electron-withdrawing effect of the trifluoromethyl group should make the α-trifluoromethylated methyl isocyanides

to be the potential active α -acidic isocyanides, which are promising synthons for the divergent synthesis of

trifluoromethylated compounds. However, to our knowledge, ⁴⁰ although α -trifluoromethylated methyl isocyanide (2,2,2trifluoroethyl isocyanide, Figure 1) was prepared more than 40 years ago,¹¹ it was mainly used as a ligand in organometallic chemistry,¹² and only two examples of Ugi-type multicomponent reactions using α -trifluoromethylated methyl isocyanides as ⁴⁵ nucleophiles were reported to date.¹³ It is probably because the β *fluoride elimination* of α -trifluoromethylated carbanion hindered the development of synthetic utilities of the CF₃-substituted isocyanides as active methylene synthons.^{3c,14}



50 Fig. 1 EWG substituted methyl isonitriles.

Recently, Hu and coworkers reported the homocoupling^{15a} and cross-coupling^{15b} of gem-difluoroalkenes via the radical reactions of relative stable α -trifluoromethylated benzylsilver intermediates, generated by a AgF-mediated process (Scheme 1, top).¹⁶ 55 Meanwhile, silver salts are powerful catalysts for the formal [3+2]-cycloaddition of isocyanoacetate.¹⁷ Therefore, we envisioned that it could be possible to use α -trifluoromethylated methyl isocyanides as precursors for the generation of α isocyano-α-trifluoromethylated carbanions catalyzed by silver 60 salts under basic conditions, thus allowing to expand the synthetic application of α -acidic isocyanides to construction of CF₃-substituted heterocycles. During the course of our study on isonitrile-based annulation,¹⁸ we herein reported a facile silvercatalyzed formal [3+2]-cycloaddition of α -trifluoromethylated 65 methyl isocyanides for the divergent synthesis of trifluoromethylated heterocycles via the new, stable and versatile α -isocyano- α -trifluoromethylated carbanion, produced by a Ag₂CO₃-catalyzed process (Scheme 1, bottom). This study on α trifluoromethylated carbanion chemistry represents the first 70 example for the efficient and practical synthesis of a wide range of trifluoromethylated five-membered nitrogen-containing heterocycles from isocyanides,¹⁹ furthermore, it could provide a facile protocol for the synthesis of useful trifluoromethylated βaminoalcohol building blocks.²⁰

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Scheme 1 Generation of trifluoromethylated alkyl silver intermediates.

Initially, the [3 + 2]-cycloaddition of 3-naphthaldehyde 1a and 1-methyl-4-(2,2,2-trifluoro-1-isocyanoethyl)benzene 2a was 5 employed to optimize the reaction conditions. It was found that, catalyzed by Ag₂CO₃ (10 mol %) and in the presence of DBU (DBU = 1,8-diazabicyclo[5.4.0]-undec-7-ene, 20 mol %) in dichloromethane at 15 °C for 45 h, the desired trifluoromethylated oxazoline 3aa was obtained in 76% yield 10 with low diasteroselectivity (Table 1, entry 1). K₂CO₃ and t-BuOK afforded lower product yield and diasteroselectivity (Table 1, entries 2 and 3). A survey of solvents identified toluene as the most suitable media, the reaction was completed in 2 h and the oxazoline 3aa was obtained in 94% yield with good $_{15}$ diasteroselectivity (d.r. = 3.5 : 1) (Table 1, entries 4-6). Decreasing the catalyst loading to 5 mol% and the amount of DBU to 10 mol% gave similar results (Table 1, entries 7 and 8). In the absence of Ag₂CO₃ or DBU, the reaction became very slow (Table 1, entries 9 and 10). For comparison, Ag₂O (entry 11), 20 AgOAc (entry 12), CuCl (entry 13), and CuI (entry 14) were less effective catalysts than Ag₂CO₃.

With the optimal conditions in hand (Table 1, entry 7), the reaction of viable aldehydes 1 with isocyanide 2a was examined; the results summarized in Table 2 revealed that the scope of the 25 aldehyde turned out to be very general. Besides 3-naphthaldehyde 1a, a wide range of substituted aryl aldehydes 1b-m reacted with isocyanide 2a to give the trifluoromethylated oxazolines 3aa-ma mostly in excellent yields and good diasteroselectivity. Compared with the electron-deficient and -neutral aryl aldehydes 1a-g, the 30 reaction of electron-rich ones 1h, 1i and 1k is slower. Heteroaryl

- aldehydes 1n-p also afforded the oxazolines 3na-pa in excellent yields. Ethyl glyoxylate 1q and cinnamaldehyde 1r also delivered the corresponding [3+2]-cycloaddition products in high yields. albeit with lower diasteroselectivity. The reactions of alkyl
- 35 aldehydes 1s and 1t with isocyande 2a gave good product yields and with moderate diasteroselectivity. In addition, the practicality

Table 1 Optimization of reaction conditions^a

1	+	NC F₃C Tol 2a	cat (x mol%) base (y mol%) solvent, 15 °C time		F ₃ C ^m N Jaaa
ent.	cat.	b.	sol.	t.	y. (%) ^{b,c}
	(x mol%)	(y mol%)		(h)	
1	$Ag_2CO_3(10)$	DBU (20)	CH_2Cl_2	45	76 (1.6 : 1)
2	$Ag_2CO_3(10)$	$K_2CO_3(20)$	CH_2Cl_2	45	58 (1.3 : 1)
3	$Ag_2CO_3(10)$	t-BuOK	CH_2Cl_2	45	62 (1.4 : 1)
		(20)			
4	$Ag_2CO_3(10)$	DBU (20)	CH ₃ CN	16	82 (1.2 : 1)
5	$Ag_2CO_3(10)$	DBU (20)	THF	2.5	82 (2.4 : 1)
6	$Ag_2CO_3(10)$	DBU (20)	toluene	2	94 (3.5 : 1)
7	$Ag_2CO_3(5)$	DBU (10)	toluene	2.5	93 (3.7 : 1)
					$(95)^{d}$
8	Ag ₂ CO ₃ (2.5)	DBU (5)	toluene	18	91 (3.6 : 1)
9	$Ag_2CO_3(5)$		toluene	45	49 (2.5 : 1)
10		DBU (10)	toluene	45	25 (2.5 : 1)
11	$Ag_2O(5)$	DBU (10)	toluene	4	93 (3.5 : 1)
12	AgOAc (5)	DBU (10)	toluene	2	90 (3.1 : 1)
13	CuCl (5)	DBU (10)	toluene	42	89 (2.7 : 1)
14	CuI (5)	DBU (10)	toluene	42	86 (2.6 : 1)

^aReaction conditions: 1a (0.1 mmol), 2a (0.15 mmol), catalyst and base in solvent (1.0 mL) at 15 °C. ^bYield was determined by ¹H NMR spectroscopy with CH₂Br₂ as internal standard. ^cd.r. was listed in the parentheses and determined by ¹H NMR spectroscopy. ^dIsolated Yields.

40 Table 2 Scope of aldehydes 1^a



^aReaction conditions: 1 (0.2 mmol), 2a (0.3 mmol), catalyst and base in solvent (2.0 mL) at 15 °C; isolated yields. ^b1.5 g 3pa was obtained. ^cAg₂CO₃ (10 mol%), DBU (20 mol%).

of this [3+2]-cycloadddtion demonstrated by the excellentyielding, gram-scale synthesis of 3pa under very mild reaction 45 conditions. The two diastereomers of **3pa** could be isolated by flash column, and the relative configuration of the trifluoromethyl oxazole **3pa** was assigned by NOSEY spectrum analysis and the structure of the minor isomer **3pa2** was unambiguously confirmed by single-crystal X-ray analysis.²¹ The stereochemical structures of the rest of the products **3** were assigned by analogy 5 with their NMR spectra.

Subsequently, the scope of this [3+2]-cycloaddition was evaluated with respect to some selected trifluoromethylated isocyanides 2; results are summarized in Table 3. The reaction tolerates isocyanides 2 bearing various R groups, such as phenyl (2b) and arther relations (2b) and such as the subset of the selected (2b) and such as the subset of the selected (2b) and such as the subset of the selected (2b) and such as the subset of the selected (2b) and such as the subset of the selected (2b) and such as the subset of the selected (2b) and such as the subset of the selected (2b) and such as the selected (2b) are selected (2b) and such as the selected (2b) are selected (2b) are selected (2b) and such as the selected (2b) are selected (2b) ar

10 (2b), para- (2c-f), meta- (2g), and ortho- substituted (2h) aryl, hetereoaryl (2i), and alkyl group (2j). The reactions of isocyanides 2 with electron-deficient (2d-f) and -neutral aryl groups (2b and 2g) are faster than the ones with electron-rich aryl groups (2c and 2h). To our delight, alkyl substituted isocyanide
15 2j also gave the products 3aj and 3cj in excellent yields when the catalyst loading was increased to 30 mol%.

Table 3 Scope of trifluoromethlated isocyanides 2^a



20 On the basis of our above observations (Table 1-3) and literature precedent on the silver-catalyzed formal [3+2]cyclization of isocyanoacetate,¹⁷ a plausible catalytic cycle is proposed (Scheme 2). The reaction starts with the formation of a complex I from silver and isocyanide 2, deprotonation by DBU to 25 produce carbanion silver intermediate II or its tautomer



Scheme 2 Plausible catalytic cycle for oxazoline formation.

α-silver isocyanide III.²² Then, the nucleophilic addition of intermediate II or III on the aldehyde 1 takes place to form ³⁰ intermediate IV, followed by cyclization to give oxazoline silver intermediate V. Finally, protonation occurs to afford the product 3 with regeneration of the catalysts, silver and DBU, for the next catalytic cycle (Scheme 2). Last year, Ma and coworkers reported a copper-triggered three-component reaction of CF₃CHN₂, ³⁵ nitriles, and aldehydes for the diastereoselective synthesis of CF₃-substituted oxazolines.²³ In their reaction, an analogue formal [3+2]-cycloaddtion of copper stablized trifluoromethylated ammonium ylide intermediate with aldehydes is proposed.

Next, the divergent synthesis of trifluoromethylated five-⁴⁰ membered heterocycles was investigated from the formal [3+2]cycloadditon of isocyanide **2a** with polar double bonds (Scheme 3). Under the standard conditions for aldehydes (Table 1, entry 7), the cycloaddition of **2a** with ketone **4** gave the oxazoline **5** with two adjacent tetrasubstituted tertiary carbon center in ⁴⁵ excellent yield. When the imine **6** and acrylonitrile **8** were used, the trifluoromethylated imidazoline **7**²⁴ and pyrroline **9** were obtained in 95% and 60% yields, respectively.



Scheme 3 Synthesis of CF₃-substituted heterocycles.

50 To test the synthetic utility of the present synthetic protocol, the transformation of the oxazole to β-amino alcohol was performed. As shown in Scheme 4, the hydrolysis of oxazoles **3pa1** and **3pa2** under acidic conditions provide the βtrifluoromethylated β-amino alcohol **10a** and **10b** in quantitative 55 yields, respectively.



Scheme 4 Transformation of oxazolines to β -trifluoromethylated building blocks.

Finally, the synthesis of the chiral trifluoromethylated ⁶⁰ oxzolines was also investigated by the asymmetric version of this [3+2]-cycloadditions (Scheme 5). Preliminary attempts revealed that **3ah** was obtained in 88% combined yield in the presence of Dixon's ligand,^{17a} although the diastereoselectivity is moderate (dr = 2.7 : 1), the enantioselectivity of both diasteroisomers is ⁶⁵ high (enantiomeric excess is 83% and 93%, respectively). Under the identical conditons, oxzoline **3aa** was obtained in 98% combined yield (dr = 2.5 : 1) with moderate but promising 61% and 72% ee of two diasteroisomers, respectively (see the Supporting Information for details).

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Scheme 5 Preliminary asymmetric studies.

In summary, a Ag-catalyzed formal [3+2]-cycloaddition of α trifluoromethylated methyl isocyanides with polar double bonds s has been developed for the expeditious synthesis of various trifluoromethylated heterocycles, such as oxazolines, imidazoline and pyrroline. Key to the success was the in situ generation of stable and versatile complex of α -isocyano- α -trifluoromethylated carbanion with silver under very mild conditions. The reaction is ¹⁰ proven to be quite practical by an excellent-yielding, gram-scale synthesis of trifluoromethylated oxazole **3pa**. In addition, the obtained oxazoles could be readily converted to useful trifluoromethylated β -amino alcohol building blocks. Preliminary studies show that asymmetric control is feasible for this [3+2]-¹⁵ cycloadditions. Further investigation of the synthetic potential of these α -trifluoromethylated methyl isocyanides are underway in our laboratory.

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