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Trifluoroacetaldehyde N-Tosylhydrazone as a Precursor of Trifluorodiazoethane in Reactions of Insertion into the Heteroatom-Hydrogen Bond

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Supporting Information

ABSTRACT: Trifluorodiazoethane is a widely explored trifluoroethylating reagent, which is suitable for the preparation of a large number of fluorine-containing organic molecules. Nevertheless, CF₃CHN₂ has some disadvantages, such as volatility, storage instability, toxicity, and explosiveness. We report the application of trifluoroacetaldehyde Ntosylhydrazone as a CF₃CHN₂ precursor capable of generating



in situ trifluorodiazoethane under mild basic conditions. Copper-catalyzed P-H, O-H, S-H, and C-H insertion reactions of trifluoroacetaldehyde N-tosylhydrazone revealed its wide applicability in the synthesis of trifluoroethyl-containing substances.

he introduction of fluorine or fluoroalkyl substituents into biologically relevant compounds has become an important tool in drug discovery.¹ Special attention is paid to trifluoromethyl-containing compounds due to the unique properties of the trifluoromethyl group, such as the high electronegativity, electron density, steric hindrance, and hydrophobic properties. 2,2,2-Trifluorodiazoethane is a versatile trifluoroethylating reagent for the preparation of a wide range of fluoroorganic compounds.

It is employed in synthetic transformations such as cyclopropanation,² [3 + 2] cycloaddition,³ reactions with carbonyl compounds⁴ and imines,⁵ heteroatom-hydrogen bond insertions,⁶ carbon-hydrogen bond insertion,⁷ carbon-boron bond insertion,⁸ and some others. The most valuable chemical syntheses are presented in Figure 1.

The preparation of 2,2,2-trifluorodiazoethane is rather complicated. It is generated by the treatment of trifluoroethylamine hydrochloride (CF₃CH₂NH₂·HCl) with sodium nitrite (NaNO₂). Pure CF_3CHN_2 is gaseous at room temperature $(M_p = 12 \text{ to } 13 \text{ °C})$ as well as explosive and toxic, so it is usually explored as a stock solution. The application of 2,2,2trifluorodiazoethane commonly requires a large excess of reagent and makes the synthetic method quite expensive. These disadvantages remain a general limitation for the wider synthetic use of this diazo compound, especially in a large-scale synthesis.

To overcome the above drawbacks, we report here the application of trifluoroacetaldehyde N-tosylhydrazone (1) as a CF₃CHN₂ precursor that is capable of generating 2,2,2trifluorodiazoethane in situ under mild basic conditions. N-Tosylhydrazones have been widely explored in organic synthesis as precursors to diazo compounds.⁹ However, trifluoroacetaldehyde-derived N-tosylhydrazone has been used as an analog of CF3CHN2 in selected publications,



Figure 1. Some applications of 2,2,2-trifluorodiazoethane.

exclusively for the preparation of CF₃-substituted pyrazolines¹⁰ and cyclopropanes¹¹ (Scheme 1A).

While this Letter was under preparation, the article of Bi and coworkers¹² appeared, reporting the successful exploration of trifluoroacetaldehyde N-(2-trifluorophenylsulfonyl)hydrazone as a trifluorodiazoethane surrogate. It was employed in the difluoroalkenylation of X-H bonds (X = N, O, S, Se) along with Doyle-Kirmse rearrangements and the cyclopropanation of alkenes. Herein we propose hydrazone 1 as a masked 2,2,2trifluorodiazoethane, which under Cu(I) catalysis enables the insertion into X-H bonds (X = P, O, S, C) to produce trifluoroethyl-containing organic molecules (Scheme 1B).

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Scheme 1. Synthetic Application of 2,2,2-Trifluorodiazoethane from Hydrazone 1



This study was started with the preparation of trifluoroacetaldehyde *N*-tosylhydrazone (1) from commercially available semiacetal CF₃CH(OH)OEt by the modified procedure disclosed by Ley.¹³ The widespread scope of copper-catalyzed X–H insertion reactions of diazo compounds prompted us to focus on this metal to probe the reactivity of 1. Copper-catalyzed insertion into the P–H bond with trifluorodiazoethane was reported in the literature by selected examples.^{6b} Thus we were interested in the elaboration of a versatile methodology for the trifluoroethylphosphonates synthesis. Diethyl phosphonate was taken as the model substrate (Table 1).

Table 1. Reaction Condition Optimization for P–H Insertion a

		H-P-OEt OEt	O F ₃ C、 _ P_OE	it
	$F_{3}C$ NNHIS —	[Cu], base	ÒEt	
	1		2a	
entry	catalyst (mol %)	base	solvent	yield ^b
1	CuI (20)	pyridine	pyridine	n.r. ^c
2	CuI (20)	Et ₃ N	CH_2Cl_2	n.r. ^c
3	CuI (20)	K ₂ CO ₃	CH ₃ CN	47
4	CuI (20)	Na ₃ PO ₄	DME	50
5	CuI (20)	NaH	THF	d
6	CuI (20)	^t BuOK	THF	d
7	CuI (20)	DBU	THF	37
8	CuI (20)	Et ₃ N	THF	95
9	CuI (20)	Et ₃ N	Et3N	77
10	$Cu(OTf)_2$ (10)	Et ₃ N	THF	17
11	$Cu(acac)_2$ (10)	Et ₃ N	THF	35
12	$Cu(F_3acac)_2$ (10)) Et ₃ N	THF	46

^{*a*}Reaction conditions: **1** (1.0 equiv), diethyl phosphonate (1.2 equiv), 70 °C or reflux (for THF and CH₂Cl₂). ^{*b*}Yield was determined by ¹⁹F NMR spectroscopy with ethyl trifluoroacetate as an internal reference. ^{*c*}No reaction. ^{*d*}Decomposition of **1** without the formation of **2a**.

Optimization studies indicated that CuI (10 mol %) was superior to the other catalysts tested (Table 1, entries 1–9 vs entries 10–12). The reaction was sensitive to the solvent and base. No reaction occurred with CuI in pyridine (weak base) or in dichloromethane (low reaction temperature) (Table 1, entries 1 and 2). The strong bases like sodium hydride and ^tBuOK caused the decomposition of 1 without the formation of **2a** (Table 1, entries 5 and 6). Triethylamine appeared to be the best base for this reaction, whereas other bases like K₂CO₃, DBU, and Na_3PO_4 were found to be less effective. The optimal reaction conditions therefore consist of reacting hydrazone 1 (1.0 equiv) with phosphonate (1.2 equiv) in THF at reflux temperature in the presence of CuI (0.2 equiv) and triethylamine (1.0 equiv). Under these conditions, diethyl 2,2,2-trifluorophosphonate (2a) was obtained in 95% NMR yield (Table 1, entry 8).

After establishing the optimal conditions for the CuIcatalyzed P–H bond insertion reaction, the reactivity of several dialkyl phosphonates was examined, and the excellent generality of this insertion process was found (Scheme 2).

Scheme 2. Scope of CuI-Catalyzed P–H Insertion of 1^{*a*}



"Yields given are for the isolated products (values in parentheses indicate the yield by 19 F NMR spectroscopy).

The reaction proceeded smoothly, giving an outcome of products 2a-f in up to 81% isolated yield. The yield was not affected much by the alkyl moiety of the starting phosphonate up to the C_6 radical. Steric hindrance of the bulky substituents prevented the formation of the desired product in the cases of dinonyl phosphonate and diisopropyl phosphonate. The P–H insertion reaction with diphenylphosphine oxide afforded a complex mixture of products.

Having in mind the results of successful reactions with P-H substrates, we supposed the formation of catalytic species containing donating ligands (trialkyl phosphite) in a coordinative sphere of copper(I) (Figure 2).





This hypothesis is supported by the fact that some other CuI-catalyzed X–H insertion reactions (X = O, N, S) failed under similar conditions. It was found that thiols, anilines, alcohols, and carboxylic acids gave low yields or traces of trifluoroethyl-substituted compounds. We suggested that copper catalysts possessing donating ligands could substantially improve the outcome of the desired products. After a short screening of Cu(I) catalytic systems, we figured out that CuBr(SMe₂) was the most effective catalyst for O–H and S– H bond insertions with carboxylic acids and thiols, respectively. Benzene was chosen as the optimal solvent for these reactions.

Carboxylic acids, either aromatic or aliphatic, appeared to be suitable substrates and were converted into the corresponding trifluoroethyl esters 3a-h (Scheme 3). Aromatic and aliphatic





carboxylic acids reacted with 1 under $CuBr(SMe_2)$ catalysis to afford products in 33–80% yield. Remarkably, the reaction tolerates phenolic hydroxyl in salicylic acid, thus leading to the trifluoroethyl salicylate (3e).

Electron-poor heteroaryl thiols reacted with 1 under the same conditions, leading to the 2,2,2-trifluoroethyl-substituted sulfides 4a-g in up to 80% yield. Fluorinated sulfides 4 can be oxidized to sulfones, which are suitable substrates for the synthesis of CF₃-substituted terminal olefins via Julia–Kocienski olefination.¹⁴ The product of the S–H insertion of thiophenol was observed only in a trace amount, using either CuI or CuBr(SMe₂) as the catalyst.

The trifluoroethylation of terminal alkynes remains an interesting challenge to date. Herein we report our first result in developing the catalytic trifluoroethylation of terminal alkynes applying *N*-tosylhydrazone **1** (Scheme 4).

Scheme 4. CuI-Catalyzed C-H Bond Insertion of 1



On the basis of the precedential work of Ma,⁷ we examined the ability of 1 to react with 4-bromo-1-ethynylbenzene (5) in the presence of CuI (10 mol %). A preliminary result was obtained via the Cu/triethylamine/MeCN system to provide the corresponding trifluoroethylated product 6 in 33% yield. The method is currently under investigation, and the results of further research will be published elsewhere.

In summary, we report the use of trifluoroacetaldehyde N-tosylhydrazone (1) as a stable precursor of CF₃CHN₂. The latter can be generated in situ under mild basic conditions that avoid working with a hazardous diazo compound. We have disclosed a direct, simple, and efficient copper(I)-catalyzed trifluoroethylation of dialkyl phosphonates, carboxylic acids, thiols, and terminal alkynes employing 1. The most significant result is the easy execution of the synthesis, which enables the rapid preparation of trifluoroethylated compounds.

ASSOCIATED CONTENT

Supporting Information

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Procedures and characterization data (PDF)

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The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

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