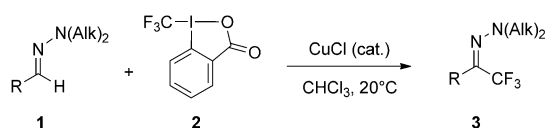


# Copper-Catalyzed Trifluoromethylation of *N,N*-Dialkylhydrazones

Etienne Pair, Nuno Monteiro, Didier Bouyssi,\* and Olivier Baudoin\*

Trifluoromethylated molecules have been drawing increasing attention from the pharmaceutical and agrochemical industries in recent years. This is mainly due to the fact that the trifluoromethyl ( $\text{CF}_3$ ) group often improves the metabolic stability and lipophilicity of biologically active compounds.<sup>[1]</sup> On this basis, the need for efficient methods for the incorporation of this group into target molecules has spurred research to discover new, practical  $\text{CF}_3$ -transfer reagents.<sup>[2]</sup> In this line, Togni and co-workers have reported new hypervalent iodine(III)  $\text{CF}_3$  compounds as mild electrophilic reagents for trifluoromethylation.<sup>[3]</sup> Recent applications of these reagents have highlighted the benefit of Lewis acid activation in terms of increasing their electrophilic reactivity.<sup>[4]</sup> For instance, the relatively cheap copper salts were found to be highly efficient  $\text{CF}_3$ -transfer catalysts.<sup>[5]</sup>

*N,N*-Dialkylhydrazones are important and versatile reagents in organic chemistry. Mainly used as synthetic equivalents of carbonyl compounds, they can also participate in free radical, pericyclic, and organometallic reactions. As well as having other interesting features, they are valuable intermediates for organic-functional-group transformations, notably as precursors to substituted hydrazines or primary amines upon reductive cleavage of the N–N bond, and as chiral auxiliaries in asymmetric synthesis.<sup>[6]</sup> Efficient protocols for the substitution of aldehyde *N,N*-dialkylhydrazones at the azomethine carbon have been developed; these protocols rely on direct reactions with active electrophiles.<sup>[7]</sup> However, to the best of our knowledge, there is no precedent for the direct incorporation of a  $\text{CF}_3$  group into these compounds.<sup>[8]</sup> Herein we report an efficient, mild procedure for the trifluoromethylation of (hetero)aromatic aldehyde hydrazones based on the use of a hypervalent iodine reagent under copper catalysis (Scheme 1).



**Scheme 1.**  $\text{Cu}^{\text{I}}$ -catalyzed trifluoromethylation of *N,N*-dialkylhydrazones. Alk = alkyl.

The first studies to determine the capability of Togni's reagent (**2**) to transfer a  $\text{CF}_3$  group to the azomethine carbon of hydrazones were conducted on *p*-nitrobenzaldehyde *N,N*-dimethylhydrazone (**1a**) as a model substrate (Table 1).

**Table 1:** Selected optimization experiments for the trifluoromethylation of *N,N*-dimethylhydrazone **1a** with **2**.<sup>[a]</sup>

Entry	Solvent	Cat. (mol %)	<i>t</i> [h]	Yield [%] <sup>[b]</sup>
1	MeOH	CuI (10)	5	59
2	MeOH	CuCl (10)	2	60
3	MeCN	CuCl (10)	2	75
4	$\text{CH}_2\text{Cl}_2$	CuCl (10)	0.75	92
5	$\text{CHCl}_3$	CuCl (10)	0.5	97 (96) <sup>[c]</sup>
6	$\text{CHCl}_3$	CuCl (5)	1	72
7	$\text{CHCl}_3$	none	20	0

[a] Reaction conditions: **1a** (0.20 mmol), **2** (0.24 mmol), catalyst, solvent (1.5 mL). [b] Determined by  $^{19}\text{F}$  NMR spectroscopy using trifluorotoluene as an internal standard. [c] Yield of the isolated product.

Initially, the reaction in the presence of 10 mol % of CuI at room temperature with MeOH as solvent, was evaluated. Gratifyingly, the desired trifluoromethylated hydrazone **3a** was obtained as the sole reaction product in a very promising 59% yield as determined by  $^{19}\text{F}$  NMR spectroscopy (Table 1, entry 1). Other combinations of solvents and copper salts were then examined. The solvent and catalyst of choice for this transformation are  $\text{CHCl}_3$  and CuCl, respectively. Under these reaction conditions, clean and full conversion of the starting material was achieved within a few minutes to give **3a** in nearly quantitative yield upon isolation (Table 1, entry 5). Notably, no reaction occurred in the absence of catalyst under otherwise identical reaction conditions (Table 1, entry 7).

With the optimized conditions established, we next investigated the effect of varying the nature of the dialkylamino group of *p*-nitrobenzaldehyde hydrazones (Table 2). Other acyclic amino groups were first examined and compared to *N,N*-dimethylhydrazone **1a**. The reaction of *N,N*-dibenzylhydrazone **1b** still furnished the expected trifluoromethylated product in acceptable yield, although a longer reaction time was required (Table 2, entry 1), whereas the reaction of hydrazone **1c**, having a much less electron-donating diphenylamino group, resulted in poor conversion and lower yield (Table 2, entry 2). Importantly, the reaction did not tolerate secondary amino groups as illustrated by the reaction of *N*-methylhydrazone **1d**. In this case, an intractable mixture of several trifluoromethylated products was

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**Table 2:** Varying the nature of the dialkylamino group.<sup>[a]</sup>

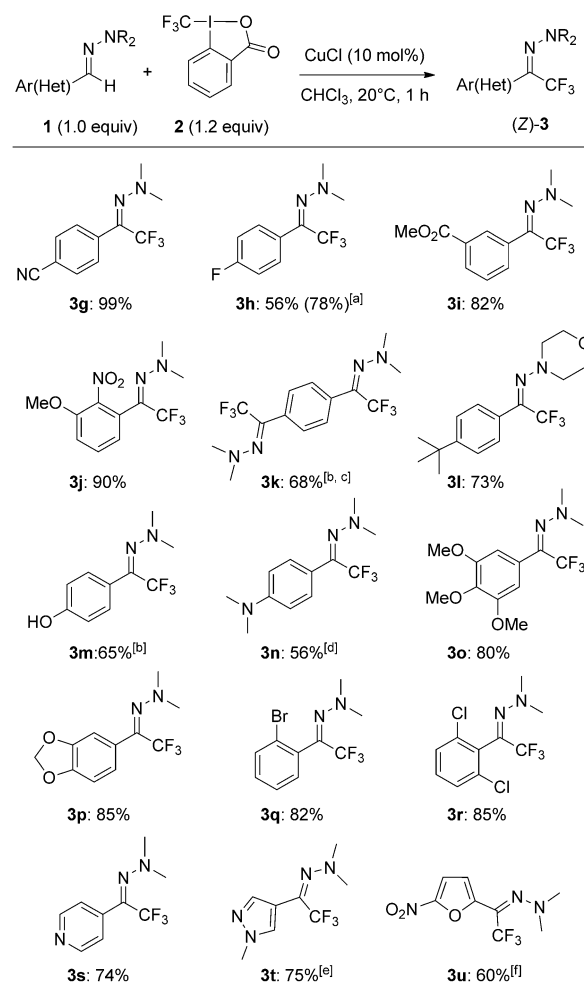
Entry	1	NR <sub>2</sub>	t [h]	Product	Yield [%] <sup>[b]</sup>
1	<b>1b</b>	NBn <sub>2</sub>	5	<b>3b</b>	61
2	<b>1c</b>	NPh <sub>2</sub>	15	<b>3c</b>	30 <sup>[c]</sup>
3	<b>1d</b>	NHMe	0.5	<b>3d</b>	— <sup>[d]</sup>
4	<b>1e</b>	1-piperidinyl	2	<b>3e</b>	88
5	<b>1f</b>	4-morpholinyl	2	<b>3f</b>	86

[a] Reaction conditions: **1** (0.35 mmol), **2** (0.42 mmol), CuCl (0.035 mmol), CHCl<sub>3</sub> (2 mL), 20°C. [b] Yield of the isolated product. [c] 55% conversion as determined by <sup>1</sup>H NMR spectroscopy. [d] All starting material was consumed. The <sup>19</sup>F NMR spectrum of the reaction mixture showed a complex mixture of products. Bn = benzyl.

obtained, although the starting materials were rapidly consumed (Table 2, entry 3). Finally, we found that hydrazones having cyclic amino groups, that is, 1-piperidinyl and 4-morpholinyl, participated efficiently in the CF<sub>3</sub>-transfer reaction to give the desired products in high yields (Table 2, entries 4 and 5).

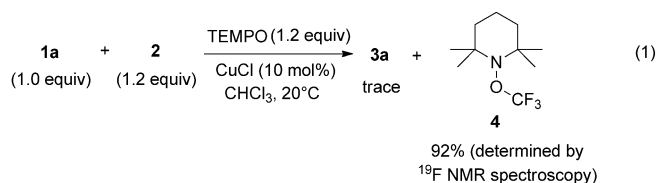
The trifluoromethylation of various (hetero)aromatic *N,N*-dialkyl hydrazones under the optimized reaction conditions was next examined, so as to gauge the scope of the reaction (Scheme 2). Good results were obtained regardless of whether the substituents on the phenyl ring were electron donating or electron withdrawing (see **3g–3r**). However, the strongly electron-donating *p*-dimethylamino group induced trifluoromethylation at the aromatic ring to a small extent (see **3n**). Various functional groups were tolerated, including nitro (see **3j**, **3u**, Table 1, and Table 2), cyano (see **3g**), ester (see **3i**), unprotected hydroxy (see **3m**), and halide (see **3h**, **3q**, and **3r**), thus offering opportunities for further diversification. Even sterically hindered hydrazones afforded the trifluoromethylation products in excellent yields, as shown with compounds **3j**, **3q**, and especially **3r**. Moreover, bistrifluoromethylation occurred in good yield (**3k**) from a substrate containing two hydrazones. Importantly, several heterocyclic hydrazones (i.e. pyridinyl, pyrazolyl, and furyl; see **3s–3u**) proved suitable substrates for the transformation, with the heterocyclic ring being left untouched. Finally, the robustness of this transformation was further demonstrated by performing the synthesis of **3p** on a half gram scale without significant decrease in yield (83%).<sup>[9]</sup> Of note, the C=N bond of the target hydrazones was determined to be exclusively *Z* configured by <sup>19</sup>F-<sup>1</sup>H HOESY NMR experiments (see the Supporting Information).

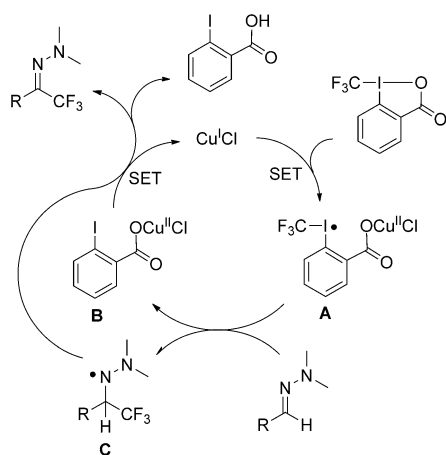
To get an insight into the possible mechanism of the catalytic reaction, we performed a radical-trapping experiment. Our standard trifluoromethylation reaction of **1a** was thus repeated in the presence of 2,2,6,6-tetramethyl-1-piperidinyl oxyl (TEMPO; 1.2 equiv). Interestingly, the formation of trifluoromethylated compound **3a** was almost completely inhibited. Instead, the TEMPO-CF<sub>3</sub> adduct (**4**)<sup>[5c,d]</sup> was formed in 92% yield, as estimated by <sup>19</sup>F NMR spectroscopy, thus suggesting the involvement of a radical mechanism



**Scheme 2.** Scope of the copper-catalyzed trifluoromethylation of *N,N*-dialkylhydrazones. Reaction conditions: **1** (0.35 mmol), **2** (0.42 mmol), CuCl (0.035 mmol), CHCl<sub>3</sub> (2 mL), 20°C. Yields are of the isolated products. [a] Volatile product; yield in brackets determined by <sup>19</sup>F NMR spectroscopy of the reaction mixture. [b] CuI was used as catalyst in CH<sub>2</sub>Cl<sub>2</sub>. [c] 1,4-benzenedicarboxaldehyde bis(*N,N*-dimethylhydrazone) was used as substrate, thus requiring 2.5 equiv of **2**. [d] A bistrifluoromethylated adduct was formed as by-product (10% yield; see the Supporting Information). [e] 1.3 equiv of **2** were used. [f] 18 h reaction time; additional CuCl (10 mol%) and **2** (0.5 equiv) were added after 15 h (68% conversion) to complete the reaction. Het = heteroarene.

[Eq. (1)]. On the basis of this experiment, we propose the mechanism depicted in Scheme 3. The reaction pathway begins with the activation of Togni's reagent (**2**) by Cu<sup>I</sup> by single-electron transfer (SET) to generate copper(II) species **A**, which acts as a CF<sub>3</sub> radical donor.<sup>[5c,d,10]</sup> Reaction with the hydrazone produces (2-iodobenzoyloxy)copper(II) chloride





**Scheme 3.** Proposed mechanism.

(**B**) and the trifluoromethylated aminyl radical intermediate **C**, stabilized by the lone pair of the adjacent nitrogen atom.<sup>[11,12]</sup> Finally, oxidation of intermediate **C** with copper(II) restores the hydrazone functional group and recycles copper(I). Interestingly, 2-iodobenzoic acid was isolated quantitatively as a co-product of the reaction by standard aqueous extraction, thus providing support for this mechanism. This compound might thus be further recycled to Togni's reagent.

Owing to the rich and diverse chemistry of *N,N*-dialkylhydrazones, the present trifluoromethylation process should prove useful for a variety of applications in organic synthesis and functional-group transformations. Some practical examples are illustrated in Scheme 4. Trifluoromethyl ketones are for instance important building blocks for the synthesis of trifluoromethyl derivatives, and have also shown interesting

may be easily restored by simple acidic treatment, as illustrated with the synthesis of trifluoromethyl ketone **5** from **3p** (Scheme 4a). Valuable CF<sub>3</sub>-substituted hydrazines may also be readily obtained by reduction of the trifluoromethyl hydrazones with lithium aluminum hydride (LAH), as shown with the synthesis of compound **6** from **3p**. In addition, trifluoromethylated amines have found applications in medicinal chemistry as non-basic amide bond surrogates.<sup>[14]</sup> Enders and co-workers reported on the asymmetric synthesis of  $\alpha$ -trifluoromethyl-substituted primary alkylamines by the 1,2-addition of organolithium reagents to the trifluoroacetaldehyde SAMP/RAMP hydrazone,<sup>[15]</sup> and subsequent SmI<sub>2</sub>-promoted cleavage of the N–N bond of the resulting hydrazines.<sup>[16]</sup> As illustrated in Scheme 4b, trifluoromethylated SAMP hydrazones such as **3v** can be easily obtained under our standard trifluoromethylation procedure starting from aromatic aldehydes. Subsequent reduction gives the corresponding benzylhydrazine **7** in 80 % isolated yield with a diastereomeric ratio of 78:22. These already promising results are expected to open a new synthetic route to enantioenriched  $\alpha$ -trifluoromethylated benzylamines and analogous heteroaromatic compounds.

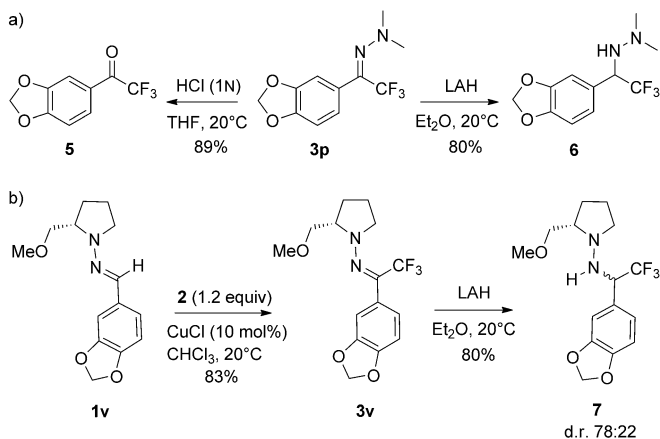
In summary, we have developed a mild, practical procedure for the trifluoromethylation of (hetero)aromatic aldehyde *N,N*-dialkylhydrazones based on the use of a readily available hypervalent iodine reagent under simple copper chloride catalysis. Further studies into the scope and limitations as well as the mechanistic understanding of this reaction are currently underway in our laboratories and will be reported as events merit.

## Experimental Section

**Trifluoromethylation of piperonal *N,N*-dimethylhydrazone:** In a glass tube, Togni reagent (**2**; 0.948 g, 3 mmol) and copper chloride (25 mg, 0.25 mmol) were successively added to a solution of piperonal *N,N*-dimethylhydrazone (0.480 g, 2.5 mmol) in CHCl<sub>3</sub> (15 mL). The reactor was flushed with argon and sealed. The reaction mixture was left to stir at room temperature for 1 hour and then washed with aq. NaHCO<sub>3</sub>. The organic layer was dried over MgSO<sub>4</sub> and concentrated in vacuo. The residue was purified by column chromatography (silica gel, appropriate mixture of cyclohexane/ethyl acetate) to afford 0.540 g (83 %) of **3p** as an oil: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 6.81 (s, 3H), 5.99 (s, 2H), 2.77 ppm (s, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 148.5, 147.7, 129.2 (q, <sup>2</sup>J<sub>C,F</sub> = 33.1 Hz), 125.5, 124.1, 122.3 (q, <sup>1</sup>J<sub>C,F</sub> = 273.3 Hz), 110.1, 108.4, 101.7, 46.8 ppm; <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):  $\delta$  = –66.9 ppm; FTIR (neat):  $\tilde{\nu}$  = 1597 cm<sup>–1</sup> (C=N); HRMS (ESI) calcd for C<sub>11</sub>H<sub>12</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub> [*M*+H]<sup>+</sup>: 261.0845, found: 261.0845.

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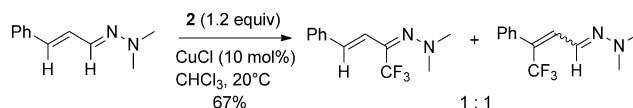
**Scheme 4.** Some potential applications in organic transformations. LAH = lithium aluminum hydride.

biological properties, notably as enzyme inhibitors. In this context, the development of new methods to access these compounds remains an area of current interest.<sup>[13]</sup> Hydrazones are obtained in high yield from the corresponding aldehydes. After trifluoromethylation, the carbonyl group

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