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Copper-Catalyzed Trifluoromethylation of Aliphatic *N*-Arylhydrazones: A Concise Synthetic Entry to 2-Trifluoromethylindoles from Simple Aldehydes

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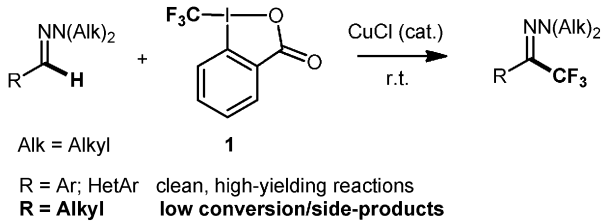
Abstract: The copper-catalyzed C(sp^2)–H trifluoromethylation of *N,N*-disubstituted hydrazones using the Togni reagent is demonstrated to proceed efficiently for aliphatic aldehyde-derived substrates. The success of the reactions relied on the choice of the *N,N*-diphenylamino group as the terminal hydrazone amino group where *N,N*-dialkylamino groups were preferred for (hetero)aromatic aldehyde-derived substrates. In addition, the trifluoromethylated *N*-arylhydrazones are shown to be ideal substrates for Fischer indole synthesis allowing a straightforward, three-step access to 2-trifluoromethylindole derivatives from simple aldehydes.

Keywords: fluorine; homogeneous catalysis; hydrazones; hypervalent compounds

Hydrazones constitute an important class of compounds known to exhibit a wide range of interesting biological activities including antitumor, antibiotic, anti-inflammatory, antimalarial and anti-HIV properties.[1] They are useful molecules for drug design, notably as promising hydrolytically-labile tethers for drug release.[2] Among other interesting features, they are readily available intermediates in synthetic organic chemistry, involved in a plethora of applications, mainly as carbonyl surrogates, but also as precursors of nitrogen-containing compounds, which include substituted hydrazines, primary amines, and nitrogen heterocycles.[3]

In recent years, CF_3-containing compounds have been receiving increased attention, notably because of their important applications as biologically active agents and new materials. They are currently at the leading edge of many new developments in the pharmaceutical and agrochemical industries.[4] In this context, there is an increasing need for synthetically useful CF_3-containing building blocks that would be easily accessible from simple starting materials. Owing to the wide synthetic versatility of hydrazones, the development of a general method for the direct C(sp^2)–H trifluoromethylation[5] of these compounds would significantly expand their application scope to include access to valuable organofluorine molecules. Although trifluoromethylhydrazones can be obtained from the corresponding trifluoromethyl ketones (TFMKs), this approach often suffers from difficulties associated with the preparation of these precursors on account of their peculiar properties.[6] We recently developed a very mild procedure for the trifluoromethylation of aldehyde *N,N*-dialkylhydrazones using the Togni hypervalent iodine reagent (**1**)[7] under copper chloride catalysis.[8] However, a significant drawback of the method lay in the low efficiencies obtained so far for aliphatic aldehyde hydrazones (**2**), the substrate scope being primarily limited to (hetero)aromatic derivatives (Scheme 1).[8a] Access to trifluoromethylated aliphatic aldehyde hydrazones (**3**) would greatly improve the synthetic utility of the methodology. For instance, these compounds are particularly attractive owing to their inherent capability to tauto-



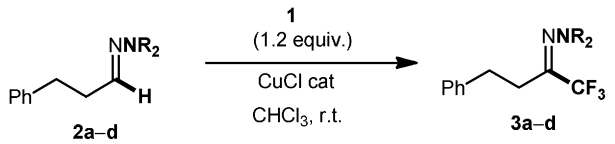
Scheme 1. Trifluoromethylation of *N,N*-dialkylhydrazones.

merize to the ene-hydrazine form making them potential precursors of a variety of valuable fluorinated heterocyclic compounds[9] through diverse cyclization processes that include, but are not limited to, the Fischer indole-type heteroannulations.[10,11]

We report herein the successful extension of the substrate scope of our hydrazone trifluoromethylation process to include aliphatic derivatives, thereby demonstrating the general utility of the method. Interestingly, the choice of *N,N*-diphenylamino as the terminal hydrazone amino group appeared to be the key to efficient promotion of these reactions, and their synthetic utility was then illustrated as a means of accessing 2-trifluoromethylindole derivatives from simple aliphatic aldehydes.

Initial attempts at trifluoromethylating *N,N*-dialkyl hydrazones using hydrocinnamaldehyde-derived precursors under our previously established reaction conditions (10 mol% CuCl, $CHCl_3$, room temperature) led to reaction mixtures containing the expected product (**3a**, **3b**) in only low amounts (Table 1, entries 1 and 2) among other undesired products. Pleasingly, we found that replacement of the *N,N*-dialkylamino with an *N,N*-diphenylamino group could suppress formation of side products and dramatically improve the yield of the desired reaction.[12] Thus, hydrocinnamaldehyde *N,N*-diphenylhydrazone underwent complete and clean conversion to the corresponding trifluoromethylated product **3c** (65% yield) (Table 1, entry 3). Furthermore, increasing the amount of catalyst had also a significant effect on the yield and rate of the reaction, furnishing 81% of **3c** (65% isolated yield) in less than two hours (Table 1, entry 4). Interestingly, reaction of the *N*-methyl-*N*-phenylhydrazone also proceeded in relatively good yield (Table 1, entry 5).

Table 1. Screening of hydrocinnamaldehyde hydrazones.



Entry	NR_2 =	Cat. [mol%]	Time [h]	Product; Yield [%][a]
1	NMe_2	10	15	**3a**; 27
2	NBn_2	10	15	**3b**; 30
3	NPh_2	10	15	**3c**; 65
4	NPh_2	20	2	**3c**; 81 (65)
5	N(Me)Ph	20	2	**3d**; 60 (53)

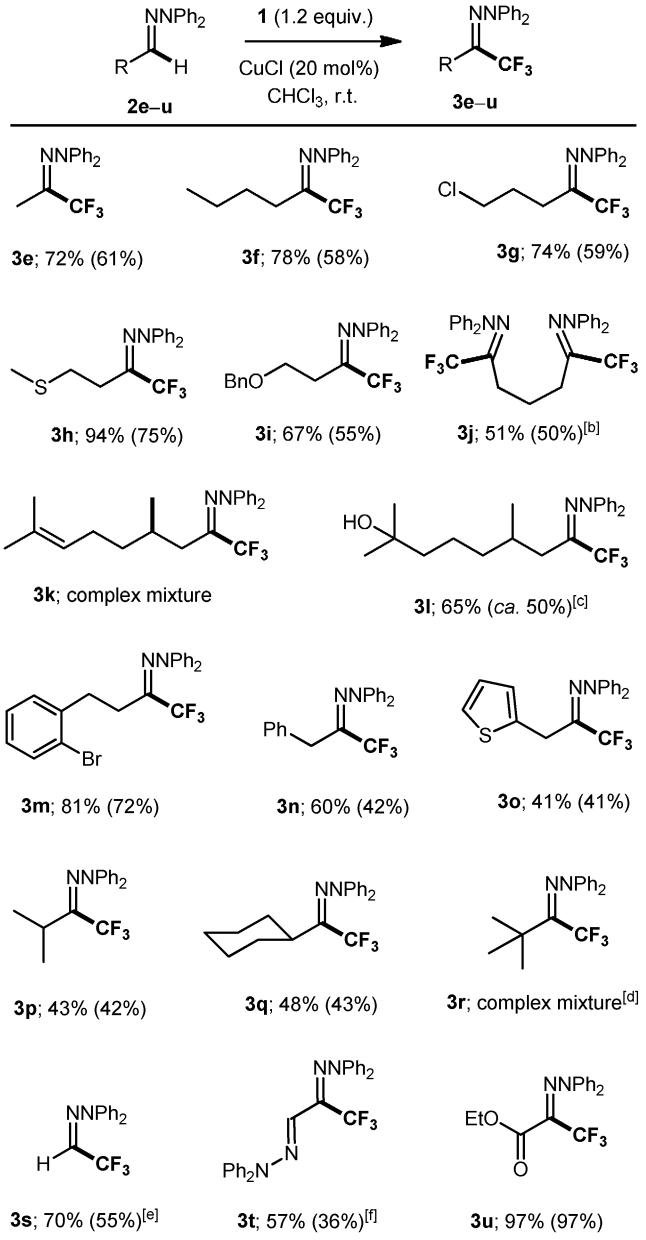
[a] Yields were determined by ^{19}F NMR spectroscopy of the crude reaction mixture using α,α,α-trifluorotoluene as an internal standard. Yields in parentheses refer to pure isolated products.

Next, the substrate scope for aldehyde *N,N*-diphenylhydrazones was explored. The results collected in Table 2 demonstrate the generality of the reaction. Linear and branched-chain primary aliphatic aldehyde derivatives were first investigated. Essentially all substrates furnished the corresponding trifluoromethylated products (**3e**–**3o**) in moderate to excellent yields and demonstrated an excellent degree of functional group tolerance. Various substituents and functional groups were tolerated, including thiomethyl (**3h**), benzyloxy (**3i**), halide (**3g**), and free hydroxy (**3l**). Moreover, bis-trifluoromethylation occurred in acceptable yield (**3j**) from a substrate containing two hydrazone moieties. Notably, no desired product (**3k**) could be isolated from the complex reaction mixture obtained for the citronellal-derived hydrazone, which probably reflects competition between two reactive functional groups (hydrazone and alkene[13]) during the trifluoromethylation process. This assertion is supported by the reaction of the saturated 7-hydroxycitronellal derivative that delivered the desired compound (**3l**) in good yield.

In addition, (hetero)aromatic derivatives of acetaldehyde hydrazones **3n** and **3o** attested to the compatibility of highly enolizable hydrazones, albeit lower yields were obtained in these cases. Moreover, it is of note that the heterocyclic ring in **3o** remained untouched. The reaction also tolerated secondary aldehyde hydrazones (**3p** and **3q**), whereas the sterically hindered pivaldehyde derivative displayed poor reactivity at the azomethine centre, giving rise to an intractable mixture of trifluoromethylated products upon increasing the reaction temperature to 50 °C. The mixture contained only small amounts of the desired product (**3r**) among several side products presumably arising from further, undesired trifluoromethylation at the electron-rich aminophenyl rings. Some non-aliphatic trifluoromethylated compounds **3s**, **3t**, and **3u**, derived from formaldehyde, glyoxal, and ethyl glyoxylate, respectively, were also synthesized to further demonstrate the broad applicability of the method. It is worthy of note that bis-trifluoromethylation was not observed in the case of glyoxal bis-hydrazone despite the use of a two-fold excess of the Togni reagent. An X-ray structure was obtained for **3e** establishing the geometry of the hydrazone C=N bond as *E* (Figure 1).[14] Finally, the robustness of this transformation was further demonstrated by performing the synthesis of **3m** on a semi-preparative 7.5 mmol scale (52% isolated yield).

Possible applications of the trifluoromethylated *N,N*-diphenylhydrazones were next investigated. Applications of great interest would include access to trifluoromethyl ketones as well as indole derivatives. Trifluoromethyl ketones are important building blocks for the synthesis of trifluoromethylated compounds[6] but have also shown interesting biological

Table 2. Substrate scope for aldehyde *N,N*-diphenylhydrazones.[a]



[a] *Reaction conditions:* **2** (0.5 mmol), **1** (0.6 mmol), and CuCl (0.1 mmol) in 3 mL $CHCl_3$ at 25 °C for 2 h. Yields were determined by ^{19}F NMR of the crude mixtures using α,α,α-trifluorotoluene as an internal standard. Isolated yields of pure compounds are given in parentheses.

[b] Glutaraldehyde bis-hydrazone as starting material; 2.4 equiv. of the Togni reagent were used.

[c] Product contaminated by trace amounts of unidentified fluorinated side-products.

[d] Reaction performed at 50 °C.

[e] The *gem*-bis-trifluoromethylated product was also obtained in 18% isolated yield.

[f] 2 equiv. of the Togni reagent were used.

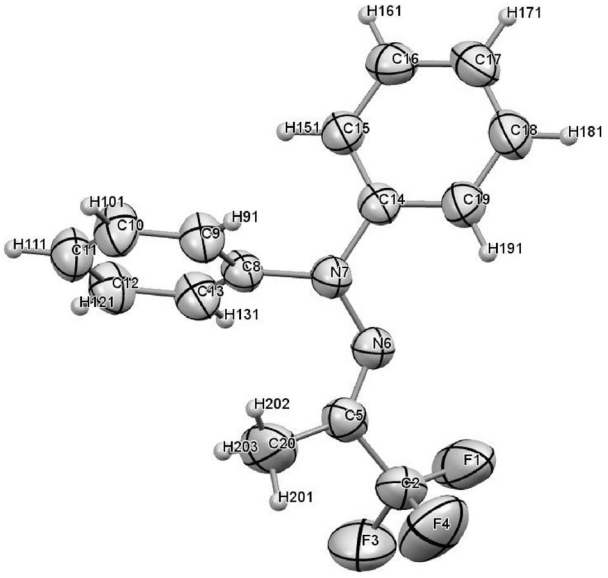
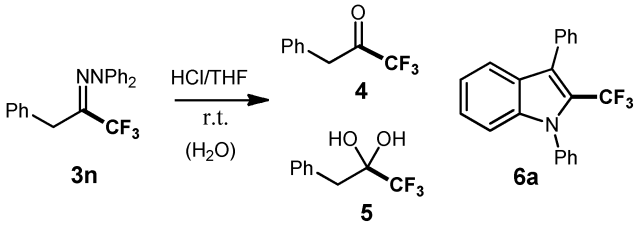


Figure 1. X-Ray representation of **3e** (ellipsoids 50% probability).

properties, notably as reversible competitive inhibitors of several classes of enzymes.[15] In this context, the development of new methods to access these valuable compounds remains an area of current interest. Although hydrolysis of arylhydrazones has, to the best of our knowledge, not been reported in the literature, the carbonyl group was expected to be restored under acidic conditions. As for 2-trifluoromethylindoles, they are core structures of pharmaceutically important molecules,[16,17] and were also expected to be accessible upon Brønsted acid treatment through Fischer-type cyclization.[18]

Our preliminary studies focused on the behaviour of phenylacetaldehyde *N,N*-diphenylhydrazone **3n** as a model substrate in hydrochloric acid medium (Table 3). Although no reaction was observed in a 1:1 mixture of 1 N HCl/THF at room temperature, the use of a higher concentration of hydrochloric acid allowed cleavage of the diphenylhydrazone protective group to yield a 1:2.5 mixture of the corresponding trifluoromethyl ketone (**4**) and its hydrate derivative **5** in a nearly quantitative combined yield (Table 3, entries 1 and 2). Ketone **4** could then be obtained in 67% isolated yield following dehydration of **5** from the mixture ($MgSO_4$, refluxing $CHCl_3$, 1 h). Diminishing the amount of water favoured formation of ketone **4** over its hydrate **5** (Table 3, entry 3) but far more interesting was the formation of 2-trifluoromethylindole **6a** (40% yield) under these relatively mild conditions. Pleasingly, repeating the reaction in the absence of moisture by using dry HCl gas led to rapid (less than 5 min), complete conversion of the hydrazone to the indole derivative, which was then isolated in a very good 79% yield. The scope of the reaction

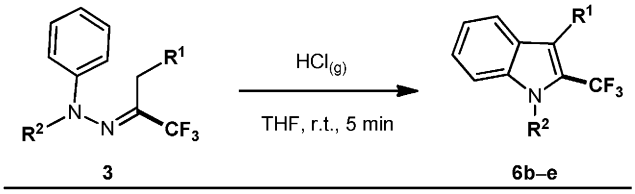
Table 3. Ketone deprotection *versus* Fischer indole cyclization under acidic conditions.[a]

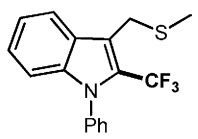


Entry	Reaction conditions	Yield [%] of **4**+**5**	Yield [%] of **6a**
1	HCl 1 N/THF (1:1), 24 h	–	–
2	HCl 6 N/THF (1:1), 24 h	95 (67[b])	trace
3	HCl 12 N/THF (1:9), 24 h	60[c]	40
4	HCl (g), THF, 5 min	<5	91 (79)

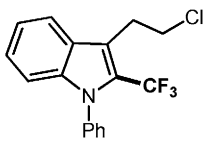
[a] Yields and ratios were determined by ^{19}F NMR spectroscopy of the crude reaction mixture using α,α,α-trifluorotoluene as an internal standard. Isolated yields of pure compounds are given in parentheses.
[b] Yield of **4** after dehydration of **5** upon heating the mixture (ratio **4**:**5** was 1:2.5) over $MgSO_4$ in refluxing $CHCl_3$.
[c] Ratio **4**:**5** was 4.5:1.

Table 4. Substrate scope for 2-trifluoromethylindoles.[a]

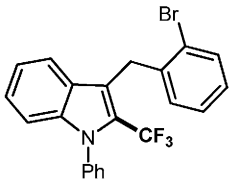




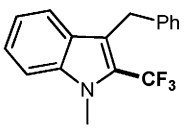
6b; 49% (49%)



6c; 96% (81%)



6d; 78% (64%)



6e; 67%[b] (59%)

[a] Reactions performed on a 0.3 mmol scale. Yields were determined by ^{19}F NMR of the crude mixtures using α,α,α-trifluorotoluene as an internal standard. Isolated yields of pure compounds are given in parentheses.
[b] 13% of the corresponding trifluoromethyl ketone were also formed.

was then briefly evaluated giving rise to an array of substituted *N*-aryl- (**6a–d**), but also *N*-alkylindoles (**6e**) in good to excellent yields (Table 4).

In summary, we have shown that our copper-catalyzed hydrazone trifluoromethylation process can also include aliphatic aldehyde derivatives as important substrates, thereby demonstrating the wide applicability of the method. Trifluoromethylated *N*-arylhydrazones have been shown to be suitable starting products in the synthesis of trifluoromethyl ketones as well as 2-trifluoromethylindole derivatives, the later becoming accessible in three steps from simple aldehydes.

Experimental Section

General Procedure 1

Preparation of trifluoromethylated hydrazones (3): In a glass tube, the Togni reagent **1** (184.6 mg, 0.6 mmol) and copper chloride (10 mg, 0.1 mmol) were successively added to a solution of the selected hydrazone (0.5 mmol) in $CHCl_3$ (3 mL). The reactor was flushed with argon and sealed. The reaction mixture was stirred at room temperature for the appropriate time and then washed with saturated sodium bicarbonate solution (3×10 mL). The organic layer was dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by flash chromatography (silica gel, appropriate mixture of pentane/dichloromethane) to afford the corresponding trifluoromethylated hydrazone.

General Procedure 2

Preparation of 2-CF_3-indoles* (6) *from trifluoromethylhydrazones: In a glass tube, the selected hydrazone (0.3 mmol) was dissolved in THF (1 mL), then HCl gas (generated through dropwise addition of concentrated H_2SO_4 to NaCl) was bubbled through the solution *via* a cannula at room temperature until a cloudy yellow solution was obtained (approximately 5 min). The reaction mixture was then washed with saturated sodium bicarbonate solution (3× 5 mL). The organic layer was dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by flash chromatography (silica gel, appropriate mixture of pentane/dichloromethane) to afford the corresponding trifluoromethylindole.

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