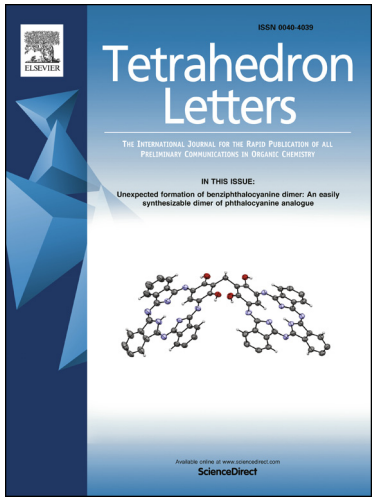

Access to Substituted Trifluoromethyl Ketones Using the Versatile Synthetic Intermediate *(E)*-1,1-Dimethyl-2-(1,1,1-trifluoropropan-2-ylidene)hydrazine

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Access to Substituted Trifluoromethyl Ketones Using the Versatile Synthetic Intermediate *(E)*-1,1-Dimethyl-2-(1,1,1-trifluoropropan-2-ylidene)hydrazine

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Dedicated to Professor Yoshito Kishi on the occasion of his 80th birthday

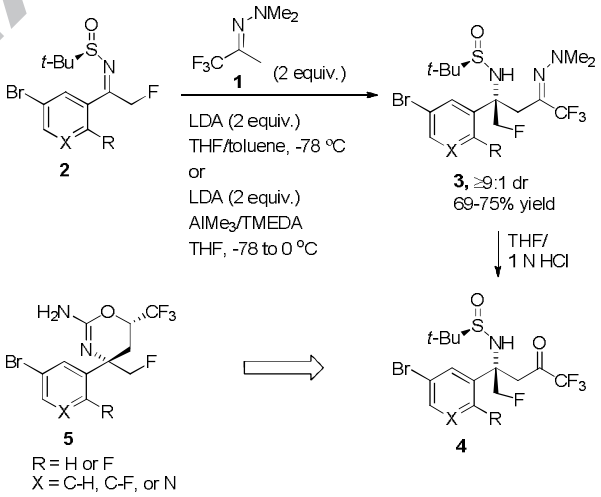
ABSTRACT: The *N,N*-dimethylhydrazone of 1,1,1-trifluoroacetone, *(E)*-1,1-dimethyl-2-(1,1,1-trifluoropropan-2-ylidene)hydrazine, has been shown to undergo a diverse set of reactions following deprotonation with *n*-butyl-lithium; including alkylation, addition to ketones and aldehydes, as well as palladium-catalyzed cross-couplings with aryl bromides. Mild hydrolysis of the *N,N*-dimethylhydrazone products from these transformations affords the corresponding trifluoromethyl ketones in good to excellent yields.

Keywords: trifluoromethyl ketone, *N,N*-dimethylhydrazone, palladium catalyst, cross-coupling, alkylation, α-arylation.

Trifluoromethyl ketones represent important intermediates for accessing trifluoromethyl-containing heterocycles and carbocycles,[1,2] as well as substituted 2-trifluoroethyl alcohols[3] and amines,[4] the latter being a known isostere for amides in pharmaceutical drug discovery. Historically, alkyl substituted trifluoromethyl ketones have most commonly been accessed either by addition of alkyl Grignard and organolithium reagents to ethyl trifluoroacetate or by reaction of the anion of ethyl trifluoroacetoacetate with an appropriate electrophile followed by ester hydrolysis and decarboxylation.[1] Over the last 20 years many alternate procedures with improved yields have been developed.[1,5] Among these, the reaction of pyridine and trifluoroacetic anhydride with acid chlorides [5a] or carboxylic acids,[5b] reactions of (trifluoromethyl)trimethylsilane with methyl esters[5c] or Weinreb amides,[5d] and condensation/decarboxylation of carboxylic acids with ethyl trifluoroacetate as described by Reeves and co-workers[5e] appear to be the most general protocols for accessing alkyl substituted trifluoroketones to date.

During the course of a medicinal chemistry program focused on the identification of a BACE1 inhibitor, a scalable, stereoselective, and high-yielding route to key intermediates with the general structure **5** was desired (Scheme 1). While **5** could be derived from trifluoromethyl ketone **4,** accessing this intermediate from *tert*-butylsulfinylimine **2** proved unsuccessful or low yielding over multiple steps using reported literature methods. However, reaction of the azaenolate of the *N,N*-dimethylhydrazone of 1,1,1-trifluoroacetone (**1**) with sulfinyl imine **2** and subsequent acid hydrolysis provided efficient access to the desired trifluoromethyl ketones (**4**) with excellent stereocontrol.[6]

Scheme 1. Stereoselective synthesis of a key intermediate toward **5**.



Notably, subsequent hydrolysis of *N,N*-dimethyl hydrazone **3** to give trifluoromethyl ketone **4** proceeded selectively under mild conditions, avoiding any hydrolysis of the *tert*-butylsulfinamide. Lastly, as hydrazones are a high-energy functional array with a risk of exothermic decomposition,[7] the thermal stability of **1** was evaluated by differential scanning calorimetry (DSC) prior to extensive use in these reactions. Highly exothermic decomposition was expected, but an onset temperature of 165 °C indicated that the material was sufficiently stable for storage at room temperature and use in reactions maintained at or below room temperature with a safety margin greater than 100 °C below the onset temperature.[8]

Given the apparent synthetic utility of **1**, along with ease of preparation (compound **1** is prepared in one step from *N,N*-dimethyl hydrazine and 1,1,1-trifluoroacetone, see ESI for details) and a suitable safety profile, we were surprised to find only a single reference from 1972 concerning the synthesis

and characterization of **1**, *(E)*-1,1-dimethyl-2-(1,1,1-trifluoropropan-2-ylidene)hydrazine.[9] Furthermore, this single report lacked any details describing its use as a reagent.[10,11] Herein, we describe our efforts to evaluate the reaction scope of **1** for use as a general reagent for the synthesis of trifluoromethyl ketones.

Azaenolates of *N,N*-dimethylhydrazones have long been reported to undergo a variety of reactions following deprotonation, including alkylation as well as addition to ketones and aldehydes.[12] To this end, *N,N*-dimethylhydrazone **1**, as a solution in THF, was deprotonated with *n*-butyl-lithium and treated with a series of electrophiles (Table 1). As expected, **1** smoothly alkylated benzyl bromide **6a** and primary alkyl iodide **6b** following deprotonation and stirring at 0 ºC to afford *N,N*-dimethylhydrazones **7a** and **7b**, respectively. Excess (2 eq.) *N,N*-dimethylhydrazone **1** was used to ensure complete conversion as any unreacted **1** was removed in the workup. Interestingly, both products were isolated in ≥ 95% selectivity for the *E*-configuration about the hydrazone double-bond.[13] Hydrolysis of **7a** or **7b** was accomplished by stirring in a 2:1 v/v mixture of MTBE or THF[14] and 1 N HCl (2 equiv.) at room temperature to afford trifluoromethyl ketones **8a** and **8b** in excellent yield.

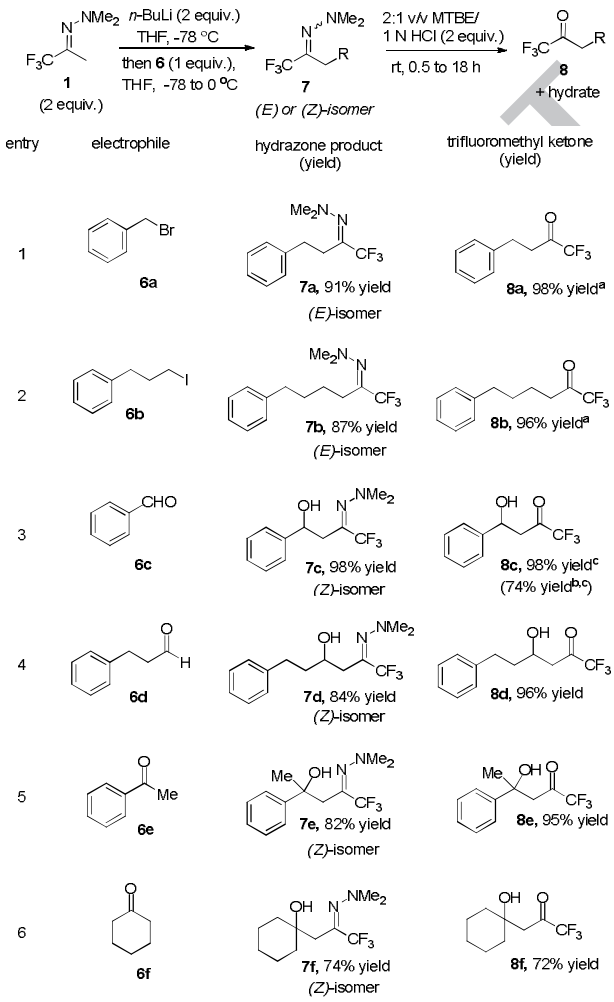
While these representative reactions demonstrate an efficient means of preparing primary alkyl substituted trifluoromethyl ketones, the multitude of existing methods in the literature[1,5] prompted us to examine reactions with the aim of accessing more scarcely reported trifluoromethyl ketone-containing products. Lithiation of **1** as before**,** followed by reaction with either aldehydes or ketones afforded *β*-hydroxy substituted trifluoromethyl ketones following hydrolysis. Thus, addition to benzaldehyde **6c** or 3-phenylpropanal **6d** provided *N,N*-dimethylhydrazone intermediates **7c** and **7d** in high yield (98% and 84%, respectively). Additionally, tertiary *β*-hydroxy *N,N*-dimethylhydrazones **7e** and **7f** were isolated upon reaction with acetophenone or cyclohexanone under identical reaction conditions in 82% and 74% yield, respectively. As with **7a** and **7b**, the isolated intermediate *N,N*-dimethylhydrazones **7c-f** proved stable to isolation and were purified under normal-phase chromatography. Contrary to **7a** and **7b**, products **7c-f** were isolated as the *(Z)*-isomer about the hydrazone double bond (diastereoselectivity >95%), presumably due to hydrogen bonding with the newly formed hydroxyl group.[15]

Initially, the selective hydrolytic cleavage of *N,N*-dimethylhydrazones **7c-f** in the presence of a potentially elimination-prone hydroxyl group was expected to present a challenge. However, gratifyingly, *N,N*-dimethylhydrazones **7c-f** underwent clean hydrolysis under identical conditions as described above to afford the corresponding *β*-hydroxyl trifluoromethyl ketones **8c-f** in high yield without any detectable elimination products.

In general, the trifluoromethyl ketones **8a**-**f** were isolated in sufficient purity directly from the hydrolysis reactions, but these could be further purified *via* silica gel chromatography.

The ketone products **8c**-**f**, however, were isolated as a varying mixtures with their hydrates, a common observation with this functionality.[1] While the reactivity would be expected to be similar for both forms, we found that stirring the hydrate-ketone mixture in CH_2Cl_2 with $MgSO_4$ at room temperature for 2.5 hours afforded the product in primarily the keto-form in most cases (>85%). Notably, as in the hydrolysis reaction, the hydroxyl group in products **8c-f** proved stable to these conditions with no detectable elimination products.

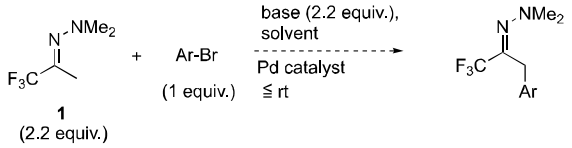
Table 1. Alkylation and addition reactions with (*E*)-1,1-dimethyl-2-(1,1,1-trifluoropropan-2-ylidene)hydrazine **1**.



[a] THF was used as the co-solvent instead of MTBE. [b] Yield after purification by silica gel chromatography. [c] Product obtained as a ~2:1 mixture of ketone to hydrate after dehydration.

Having successfully demonstrated the versatility of the lithium azaenolate of **1** for alkylation and carbonyl addition reactions, we endeavored to further expand the scope of reactivity**.** Specifically, the palladium catalyzed cross-coupling of **1** with aryl halides would represent a useful reaction for later-stage installation of this functionality in a multi-step sequence (Scheme 2). While the palladium-catalyzed cross-couplings of ketone and ester enolates with aryl halides is well known,[16] to the best of our knowledge, no reports detailing the direct cross-coupling of azaenolates of hydrazones with aryl halides to afford α-substituted hydrazones have been published to date.

Scheme 2. Proposed palladium cross-coupling of *N,N*-dimethylhydrazone **1** with aryl bromide.



Recalling the earlier safety studies with **1**, cross-coupling reaction conditions were therefore sought that would avoid the need for heating. To this end, the azaenolate of *N,N*-dimethylhydrazone **1** was treated with bromobenzene in the presence of a palladium catalyst in toluene at room temperature (Scheme 2). Initial studies were conducted with [(*tert*-Bu_3P)$PdBr]_2$ given the success with this catalyst in room temperature α-arylation of ester enolates by Hartwig and co-workers[17a,b] as well as colleagues within Amgen.[17c] However, the reaction using this catalyst (5% palladium catalyst loading) at room temperature for 18 hours provided low conversion (≤ 40%) of the cross-coupled product **9a.**

A much more efficient coupling was observed using the third generation *tert*-ButylX-Phos palladacycle precatalyst. Developed by Buchwald and co-workers,[18] this precatalyst has been successfully employed in the α-arylation of the enolate of *tert*-butyl acetate with aryl chlorides at rt.[19] Using this precatalyst, α-arylations of **1** were complete at rt within 1.5 h following deprotonation with *n*-butyl-lithium, affording isolated products in good to excellent yields utilizing several aryl bromides with diverse electronic properties (Scheme 3).

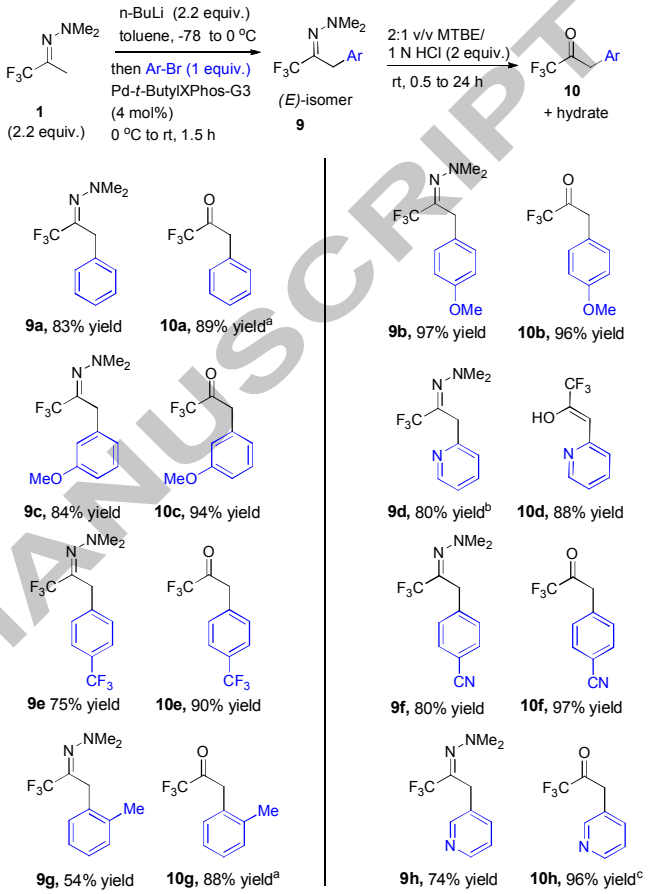
While the initial substrate phenyl bromide afforded the desired hydrazone **9a** in 83% yield (Scheme 3), more electron rich aromatic substrates afforded higher yields such as methoxy-substituted products **9b** (97% yield) and **9c** (84% yield). Somewhat lower yields were obtained using electron withdrawing substrates, affording products **9e** and **9f** as well as pyridines **9d** and **9h** (74-80% yield). Arylation with the sterically encumbered 2-bromo toluene gave **9g** in a more modest yield (54%), even with extended reaction time (2.5 h). Notably, each α-aryl hydrazone product **9a-h** was isolated as the *(E)*-isomer.[13] In all cases, neither side-products originating from α,α-diarylation nor C-N coupling at the hydrazone nitrogen was observed. In similar fashion as the reported Pd-catalyzed α-arylation of ketones and esters, reactions in THF failed to afford any product whereas the use of toluene as the reaction solvent proved optimal. However, in notable contrast to the aforementioned references, the use of LiHMDS as the base, even as a solution in toluene, did not afford any cross-coupled product.

Hydrolysis of **9a-h** proceeded as expected using the standard conditions as described previously using HCl and MTBE or THF to afford the α-aryl trifluoromethyl ketones **10a-h** in excellent yield. As previously observed, the trifluoromethyl ketones were isolated as varying mixtures with their hydrates. Performing the identical dehydration protocol using CH_2Cl_2 and $MgSO_4$ as described above allowed for conversion of the product to primarily the keto-form in most cases.

Additionally, in order to evaluate potential hazards of the high-energy functionality present in these products, a small subset of the hydrazone intermediates (i.e., **7b**, **7e**, **9f**) were analyzed by DSC for thermal stability. All three compounds were found to have exothermic decompositions well above 100 °C, indicating a very low risk of instability while manipulating these compounds at ambient temperature or below.[20]

Thus far, the reaction scope of **1** was directed at synthesizing α-monosubstituted trifluoromethyl ketones with the intermediate hydrazone serving as a latent ketone-precursor. The intermediate *N,N*-dimethylhydrazones as described above, however, provide useful intermediates for additional

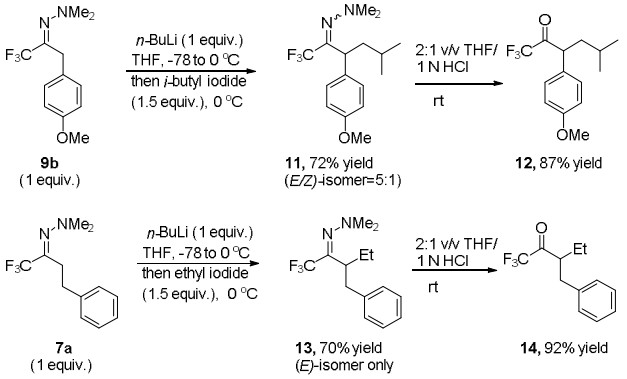
Scheme 3. Scope of cross-coupling reactions of **1** with aryl bromides using Pd-*t*-ButylXPhos-G3 precatalyst.



[a] THF used as co-solvent instead of MTBE. [b] Product isolated as a 2:1 mixture with the ene-hydrazine tautomer. [c] Product obtained as a ~2:1.4 mixture of ketone to hydrate after dehydration.

functionalization.[21] In this context, two representative hydrazones, **9b** and **7a**, were further alkylated with *iso*-butyl iodide and ethyl iodide respectively, using a similar deprotonation-alkylation sequence to provide bis-α-substituted hydrazones **11** and **13** in good yields (Scheme 4).

Scheme 4. Alkylation of substituted *N,N*-dimethyl-trifluoromethyl hydrazones.



While *N,N*-dimethylhydrazone **13** was formed exclusively as the *(E)*-isomer, compound **11** was observed to be a 5:1 mixture of *E*:*Z*-isomers about the hydrazone double bond. Both products afforded the corresponding α-disubstituted trifluoromethyl ketone **12** and **14** in good yield following our standard hydrolysis protocol (THF used as the co-solvent).

In conclusion, *(E)*-1,1-dimethyl-2-(1,1,1-trifluoropropan-2-ylidene) hydrazine **1** has been shown to be a versatile reagent for alkylation and addition reactions, as well as Pd-catalyzed cross-coupling reactions. Mild and chemoselective hydrolysis of these products afforded highly functionalized trifluoromethyl ketones in high yield.[22] Additionally, the stable *N,N*-dimethylhydrazone intermediates can undergo further elaboration prior to hydrolysis affording opportunities for a broader scope of α-disubstituted products. Finally, the unprecedented Pd-catalyzed cross-coupling of the azaenolate of **1** with aryl bromides may represent a new, general substrate class for Pd-catalyzed cross-coupling reactions which warrants further investigation.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge.

Experimental procedures, characterization data including Differential Scanning Calorimetry results and thermograms, and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(8) See the ESI for DSC results of **1**, as well as the starting reagent 1,1-dimethylhydrazine and the completed reaction mixture for the synthesis of **1**.

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(12) For a comprehensive review of hydrazone chemistry, see: Lazny, R.; Nodzewska, A. *Chem. Rev.* **2010**, *110*, 1386-1434.

(13) NMR NOESY experiments were used to determine the configuration.

(14) While MTBE was initially used as the organic co-solvent, much faster rates of hydrolysis were observed using THF.

(15) NMR HOESY experiments were used to determine the *(Z)*-configuration.

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(20) These results and associated thermograms may be found in the ESI.

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(22) In several cases with large aliphatic substrates (**8a**, **8b**, **12**, and **14**), the desired product was isolated directly as the ketone with the absence of any hydrate making the second dehydration step unnecessary.

Highlights

- Alkyl substituted trifluoromethyl ketones are synthesized in high yield.
- Unique -hydroxy trifluoromethyl ketones can be prepared.
- First example of a palladium catalyzed -arylation of a hydrazone.
- Reactions are operationally simple and high yielding.