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A Weinreb amide approach to the synthesis of trifluoromethylketones†

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A novel route to access trifluoromethylketones (TFMKs) from Weinreb amides is reported. This represents the first documented case of the Ruppert–Prakash reagent (TMS–CF_3) reacting in a constructive manner with an amide and enables synthesis of TMFKs without risk of over-trifluoromethylation.

The trifluoromethyl group (–CF_3) is of great interest to the medicinal chemistry community due to its ability to drastically alter the physiological and chemical properties of compounds.[1] While many methods for the introduction of this functionality into organic molecules have been developed, few compare to the versatile nature of the Ruppert–Prakash reagent (TMS–CF_3).[2] This reagent has been used in the construction of many trifluoromethylated synthons including α-trifluoromethyl alcohols,[3] benzotrifluorides,[4a] trifluoromethyl heteroarenes,[4b] trifluoromethylamines,[4c] aryltrifluoromethyl-sulfides,[4c] and trifluoromethyl alkanes,[4c] alkenes[4d] and alkynes.[4e] One moiety that is relatively difficult to access *directly* using TMS–CF_3 is the trifluoromethylketone (TFMK). TMFKs are highly valuable species as synthons in the construction of other fluorinated compounds[5] and as potent enzyme inhibitors.[6]

Current methods for the preparation of TFMKs utilize three major routes: alkylation of trifluoroacetic acid (TFA) derivatives (*via* organometallic reagents),[7] oxidation of α-CF_3 alcohols,[8] or, more recently, nucleophilic substitution of carbonyl derivatives utilizing TMS–CF_3.[9,10] Alkylation is the more traditional route and, while several successful strategies have been developed, concomitant exhaustive alkylation or Meerwein–Ponndorf–Verley type reductions can lead to complications. Conditions to avoid some of these problems have recently been developed.[7e] Routes exploiting oxidation can also prove difficult. α-Trifluoromethyl alcohols are notoriously difficult substrates to oxidize and, while periodinane-based methods are successful,[11] attempts using standard oxidants (metal-based or DMSO-based) are often met with poor yields or failure.[8,12,13]

Trifluoromethylation of an activated carbonyl derivative with TMS–CF_3 *via* nucleophilic substitution is another viable option to access TFMKs. While acid chlorides and anhydrides are known to be too reactive for mono-trifluoromethylation, Prakash[9] and Shreeve[10] have published independent reports detailing procedures for direct acyl substitution of esters using TMS–CF_3. While significant achievements, both methods have drawbacks. Prakash's hinges on the use of anhydrous reaction conditions to avoid quenching the –CF_3 anion. Additionally, prolonged reaction times and very low temperatures are necessary to avoid double-addition.[9] Shreeve improved on this by using CsF as an initiator and conducting most reactions solvent-free.[10] However, problems with exotherms limit its scalability.

In 1981, Weinreb and co-workers reported a method for using *N*-methoxy-*N*-methylamides (now known as Weinreb amides) to prepare ketones directly without the risk of over alkylation.[14] The importance of this discovery has become clear based on the regularity in which they are used in synthesis and the numerous methods developed for their preparation.[15] A lesser-known report detailed the successful synthesis of a TFMK using the Weinreb amide of trifluoroacetic acid when treated with a Grignard reagent.[16] This demonstrated that in an acyl substitution reaction, the *N*-methoxy-*N*-methylamine group will be eliminated preferentially over the CF_3 moiety. With this important precedent, we theorised that Weinreb amides could serve as viable candidates for trifluoromethylation to synthesise TFMKs *directly* using TMS–CF_3, despite the established lack of reactivity of amides with TMS–CF_3.[17] Here we detail the results of our investigation.

We began our investigation by screening the reaction between **1a** and TMS–CF_3 using a variety of fluoride initiators (Table 1). Initially we used 1.3 equivalents of TMS–CF_3, this being the typical loading for the trifluoromethylation of carbonyl compounds.[3] Less aggressive fluoride sources, NaF and KF were not effective initiators for the reaction, likely due to solubility issues (entries 1 and 2). However, use of more aggressive initiators, TBAF and CsF, did lead to the desired TFMK **3a**, albeit in suboptimal conversion (entries 3 and 4). Extended reaction times failed to improve conversion. ^{1}H-NMR spectroscopy of the crude reaction mixture showed the formation of intermediate **2a**. We postulated that **2a** could either eliminate to give the desired ketone or revert to the starting material.[18] We decided to optimise the conditions for formation of **2a** then follow with a cleavage step to yield the TFMK. We screened several solvents with varying polarities (entries 5–7), theorising that

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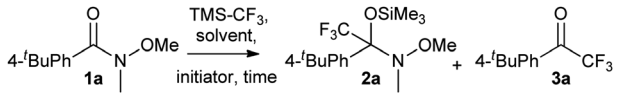
Table 1 Optimisation of reaction conditions[a]



Entry[a]	Solvent	Initiator	TMS–CF_3 (eq.)	Time (h)	**2a** (%)	**3a** (%)
1	THF	NaF	1.3	17	—	—
2	THF	KF	1.3	17	—	—
3[b]	THF	TBAF	1.3	17	—	12
4	THF	CsF	1.3	17	—	55
5[c]	MeCN	CsF	1.3	17	—	—
6[c]	CH_2Cl_2	CsF	1.3	17	11	—
7[c]	Toluene	CsF	1.3	17	70	—
8[c]	Toluene	CsF	1.0	17	63	—
9[c]	Toluene	CsF	2.0	17	84	—
10[c]	Toluene	CsF	3.0	17	90	—
11[c]	Toluene	CsF	6.0	17	91	—
12[d]	**Toluene**	**CsF**	**2.0**	**24**	**95 (81)**[e]	—

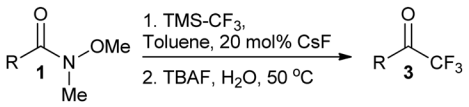
[a] Reaction conditions: **1a** (1.0 mmol), initiator (20 mol%), TMS–CF_3, solvent (1.5 mL) at rt. [b] 5 mol% initiator. [c] 0.5 mL solvent. [d] Performed on a 5 mmol scale in 2.5 mL solvent, cooled 0 °C to rt. [e] Isolated yield.

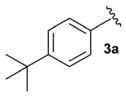
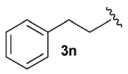
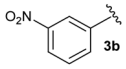
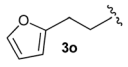
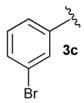
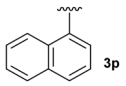
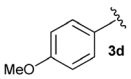
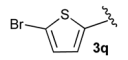
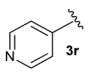
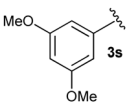
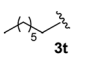
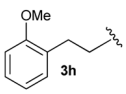
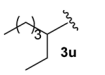
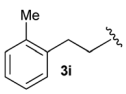
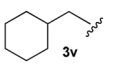
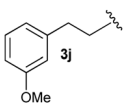
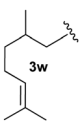
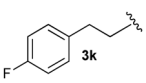
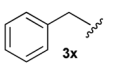
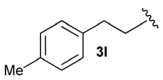
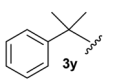
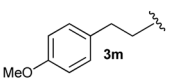
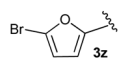
altering the solvent polarity could shift the reaction pathway to favour **2a**. A nonpolar solvent, toluene, gave the best conversion to the silylated intermediate (entry 7). Next, variation of the TMS–CF_3 loading was examined to improve the overall conversion to **2a** (entries 8–11). While 2 eq. did not give the highest conversion (entry 9 *vs.* entries 10 and 11) it was the most practical for scale up. We were pleased to find that, upon scale up and at slightly extended reaction times, we achieved near quantitative conversion to **2a** (entry 12). This intermediate proved stable enough to be isolated in excellent yield and characterised (see ESI†).

Seeking to obtain the TFMK from this compound, we next attempted to cleave **2a** to give **3a** by elimination of the amino substituent. Believing this silyl ether to be difficult to cleave because of its surprising inherent stability and steric bulk, we initially used a stoichiometric loading of TBAF in THF. We also added an equal volume of water to serve as a proton source for the departing amino group. However, we found that we obtained minimal conversion to the TFMK. Upon heating to 50 °C, we obtained complete conversion to the desired TFMK in 2 h. However, we wanted to see if we could reduce the loading of TBAF and the amount of water used without compromising the rapidity and completeness of cleavage. In the case of **2a**, 10 mol% TBAF with an equal volume of water could be used without loss in conversion. These reduced loadings were later found not to be compatible with all intermediates screened; hence we utilised stoichiometric conditions for this study.

With optimised conditions in hand for both the conversion of the Weinreb amide to the silyl intermediate and its subsequent cleavage, we next explored the substrate scope of our protocol. An array of aryl Weinreb amides (Table 2, entries 1–4, 16, 19) were compatible with our reaction conditions giving good to excellent yield of their corresponding TFMKs. Three exceptions were rings bearing *o*-substituents to the Weinreb functionality (entries 5–7). Since **1g** and **1f** (entries 6 and 7) are electronic antagonists, we concluded that their lack of reactivity can be attributed to the steric bulk of these groups. This was confirmed by placement of a nonpolar group at the *ortho* position (entry 5). *Ortho*-substitution likely deters coordination of the amide to TMS–CF_3.[2,19] By distancing the amide away from the *ortho*-substitutent

Table 2 Trifluoromethylation of Weinreb amides[a]



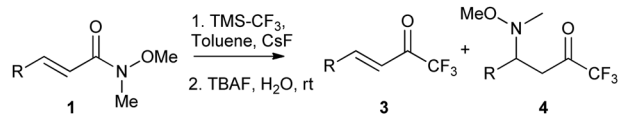
Entry	R	Yield[b] (%)	Entry	R	Yield[b] (%)
1		81	14		76
2		78	15		51
3		72	16		84
4		88	17		63
5		—	18		90[d]
6		—	19		99
7		—[c]	20		59
8		75	21		—
9		66	22		61
10		81	23		48
11		61	24		Decomp.
12		78	25		—
13		73	26		66

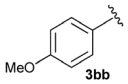
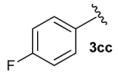
[a] Reaction conditions: *Addition*: Weinreb amide (1 eq.), TMS–CF_3 (2 eq.), CsF (0.2 eq.), toluene (2 M or 0.5 M), 24 h. *Cleavage*: TBAF (1 eq., 1 M in THF), H_2O (equal vol. with respect to TBAF) 50 °C, 2 h. [b] Isolated yield after purification. [c] 25% conversion by ^{1}H-NMR to TFMK. [d] Isolated yield of stable hydrate.

reactivity was returned and we obtained a good yield of the corresponding TFMK (entry 8).

Various aliphatic (entries 9–15, 20–25) and heterocyclic Weinreb amides (entries 17, 18 and 26) were then screened. Those with α-substitution proved incompatible (entries 21 and 25),

Table 3 Trifluoromethylation of α,β-unsaturated Weinreb amides[a]



Entry	R	Yield of 3 (%)	Ratio of 3 : 4
1	 3aa	22	25 : 75[b]
2	 3bb	47	55 : 45[b]
3	 3cc	41	41 : 59[b]
4	 3dd	51	71 : 29[b]
5	 3ee	—	—

[a] Reaction conditions: *Addition*: Weinreb amide (1 eq.), TMS–CF_3 (2 eq.), CsF (0.2 eq.), toluene (2 M), 24 h. *Cleavage*: TBAF (1 eq., 1 M in THF), H_2O (equal vol. with respect to TBAF) rt, 2 h. [b] Ratio determined by ^{1}H-NMR spectroscopy.

which likely can be explained using a similar steric argument as the *o*-substituted substrates. By moving the substituent to the β-position (entry 23), restricting its conformation (entry 22), or removing it entirely (entry 20), the reaction proceeds easily, giving fair to good yields of the desired TFMKs. Of note is the α-phenyl substituted substrate (entry 24) whose decomposition could be attributed to the enhanced acidity of its α-protons. Furyl, thiophenyl, and pyridyl systems were all compatible with our optimised conditions, affording good yields of the corresponding TFMKs (entries 15, 26, 17, and 18 respectively).

Finally, α,β-unsaturated Weinreb amides were explored as substrates. Using **1aa** as a model substrate, we obtained a low yield of the desired TFMK **3aa** (Table 3, entry 1). However, ^{19}F and ^{1}H NMR analysis revealed an additional TFMK product, namely **4aa**. Formation of **4aa** can be rationalised by Michael addition of the displaced *N*,*O*-dimethylhydroxylamine anion into the highly electrophilic alkene of **3aa**. Other α,β-unsaturated Weinreb amides showed similar reactivity with differences in the ratio of **3** : **4** (entries 2–4). Interestingly, non-conjugated α,β-unsaturated Weinreb amide **1ee** afforded no reaction (entry 5).

In conclusion, we have disclosed the first example of TMS–CF_3 reacting with an amide functionality to furnish a TFMK. The reaction is compatible with a range of Weinreb amides, affording moderate to excellent yields of the TFMK products without formation of the over-trifluoromethylated products. While most Weinreb amides react readily, sterically encumbered amides fail to react appreciably, if at all. The use of α,β-unsaturated Weinreb amides is complicated by the formation of the Michael adduct of the TFMK and *N*,*O*-dimethylhydroxylamine, but the TFMK and this adduct are separable and can be isolated in fair yield.

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