Solkane® 365mfc is an environmentally benign alternative solvent for trifluoromethylation reactions†

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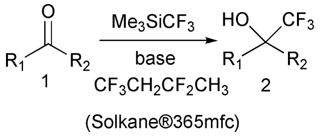
Solkane® 365mfc is introduced for the first time as a new, environmentally benign alternative solvent for nucleophilic trifluoromethylation reactions.

Trifluoromethylated compounds are finding widespread application in pharmaceuticals, agrochemicals, and liquid crystals due to their extreme properties.[1] Among various methodologies available for the preparation of trifluoromethylated compounds, the nucleophilic trifluoromethylation reaction using Ruppert's reagent ((trifluormethyl)trimethylsilane, Me_3SiCF_3) is the most direct method for introducing a CF_3 unit into synthetically useful carbonyl compounds and others.[2] Me_3SiCF_3 was developed by Ruppert *et al.*,[3] and in 1989, Prakash *et al.* found tetrabutylammonium fluoride (TBAF) to be an effective catalyst for the trifluoromethylation reaction of carbonyl compounds with Me_3SiCF_3.[4] Me_3SiCF_3 is now becoming popular as the Ruppert–Prakash reagent and considerable efforts have been devoted to the development of efficient catalytic systems for this process.[2] Although Me_3SiCF_3 was initially too expensive to afford scaling up the corresponding reaction, TOSOH-FTEC INC. developed a process to make the reagent in up to ton quantities at about one-fifth of the price using a contained system avoiding problems with the ozone-depleting starting material.[5] Since then, Me_3SiCF_3 has been widely used in both academia and industry.[6–8] Among several solvents used for the trifluoromethylation reaction by Me_3SiCF_3, the most commonly used is DMF,[7] followed by ether solvents and dichloromethane.[6,8] An especially beneficial effect caused by DMF is believed to be responsible for the coordination of the silicon atom on Me_3SiCF_3 to stabilize the hypervalent silicate species.[7e,h,i,8d] However, these solvents have some drawbacks, such as toxicity and peroxide formation. Increasingly tighter restriction on the use of organic solvents in industrial synthesis[9] led us to search for an environmentally benign alternative solvent for the trifluoromethylation reaction. Although solvent-free conditions seem to be suitable for green chemistry, in most cases, a solvent is often required to assist in working-up processes and transporting of materials.[10] The use of ionic liquids as alternative reaction media for organic chemistry is another solution.[11] Kim and Shreeve succeeded in Cu(I)-mediated nucleophilic trifluoromethylation in ionic liquid media by the use of original ionic liquids; in comparison, the corresponding trifluoromethylation did not proceed in a commercially available imidazolium ionic liquid, [bmim][PF_6].[12] Fluorous technology is also attractive from a green chemistry point of view; however, issues such as the environmental impact of fluorous chemicals are a matter of debate.[13] Curran and co-workers introduced benzotrifluoride and related compounds as new solvents for traditional organic synthesis and for fluorous synthesis.[14] In this paper, we report that a hydrofluorocarbon, Solkane® 365mfc (1,1,1,3,3-pentafluorobutane) is a potentially useful alternative solvent for trifluoromethylation reactions (Scheme 1).



Scheme 1 Solkane® 365mfc is an environmentally benign alternative solvent for trifluoromethylation reactions of carbonyl compounds.

Solkane® 365mfc, is a non flammable liquid developed by Solvay Fluor GmbH. Solkane® 365mfc has no impact whatsoever on the ozone layer, and it passed all the necessary toxicological tests successfully.[15,16] It is used as an insulating and blowing agent for polyurethane foams, whose main uses are thermal insulation of residential and industrial buildings as well as cold storage. Solkane® 365 mfc is now produced in a pilot plant with a capacity of several hundred tons per year. Despite its environmentally attractive properties, no examples of its use for organic reactions are available. Due to the specific character that fluorinated compounds tend to dissolve well in fluorinated solvents, Solkane® 365mfc might be an ideal solvent for trifluoromethylation reactions.

The catalyst/solvent systems represented by LiOAc/DMF,[7e] TBAF/THF[4] and P^tBu_3/DMF[7i] act as a good trigger for the trifluoromethylation of aldehyde **1a** with Me_3SiCF_3; however, the catalysts were completely useless in Solkane® 365mfc (Table 1, runs 1–6), and even TBAF was ineffective for this transformation in Solkane® 365mfc, despite its big success as a catalyst for the trifluoromethylation reaction, and the desilylated **2a** was obtained only in 23% yield (run 4). The K_2CO_3/DMF system is also quite effective for this type of reaction (run 7), but the result using Solkane® 365mfc was not comparable to the reported one.[7h] When we used a catalytic amount of K_2CO_3 in Solkane® 365mfc, the desired product was obtained in 64% yield after stirring for 17 h (run 8). We next focused our attention on the use of purely inorganic bases as catalysts. Reaction of **1a** with Me_3SiCF_3 in the presence of catalytic amounts of NaOH in Solkane® 365mfc at rt for 4 h gave **2a** in 83% yield, confirming

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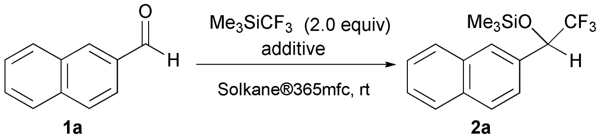
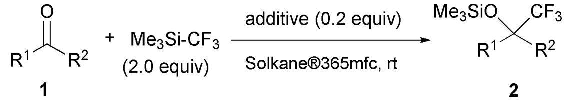
Table 1 Trifluoromethylation of Naphthyl aldehyde (**1a**) in Solkane® 365mfc



Run	Solvent	Additive (equiv.)	Time	Yield (%)[a]
1	DMF	LiOAc (0.05)	10 min	98[b]
2	Solkane®	LiOAc (0.2)	24 h	trace
3	THF	TBAF (0.2)	90 min	52
4	Solkane®	TBAF (0.2)	45 min	23
5	DMF	P^tBu_3 (0.1)	30 min	99[c]
6	Solkane®	P^tBu_3 (0.2)	24 h	trace
7	DMF	K_2CO_3 (0.2)	5 min	85[d]
8	Solkane®	K_2CO_3 (0.2)	17 h	64
9	Solkane®	NaOH (0.2)	4 h	83
10	Solkane®	KOH (0.2)	20 min	96
11	Solkane®	$CsOH{\cdot}H_2O$ (0.2)	10 min	94
12	Solkane®	$CsOH{\cdot}H_2O$ (0.1)	10 min	97
13	Solkane®	CsF (0.2)	20 min	99
14[e]	Solkane®	KOH (0.2)	5 h	99.5

[a] Isolated yield by silica-gel column chromatography. [b] See ref. 7g. [c] See ref. 7i. [d] See ref. 7h. [e] The reaction was performed on a slightly large scale and the product **2a** was isolated without using any solvent by filtration and distillation. Solkane® 365mfc was recovered in 89% yield. See ESI.†

Table 2 Trifluoromethylation of aldehydes and ketones with Me_3SiCF_3 in Solkane® 365mfc



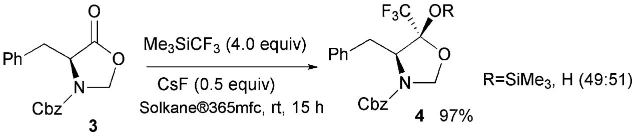
Entry	1	R^1	R^2	Additive	Time/min	2	Yield (%)[a]
1	**1a**	2-naphthyl	H	KOH	20	**2a**	96
2	**1b**	1-naphthyl	H	KOH	30	**2b**	92
3	**1c**	Ph	H	KOH	15	**2c**	91
4	**1d**	4-MeC_6H_4	H	KOH	60	**2d**	90
5	**1e**	2-MeOC_6H_4	H	$CsOH{\cdot}H_2O$[b]	60	**2e**	80
6	**1f**	3-MeOC_6H_4	H	KOH	60	**2f**	92
7	**1g**	4-MeOC_6H_4	H	KOH	25	**2g**	94
8	**1h**	4-BrC_6H_4	H	$CsOH{\cdot}H_2O$[b]	20	**2h**	88
9	**1i**	$4\text{-NO}_2C_6H_4$	H	CsF	20	**2i**	94
10	**1j**	PhCH=CH	H	$CsOH{\cdot}H_2O$[b]	20	**2j**	84
11	**1k**	$PhCH_2CH_2$	H	CsF	20	**2k**	82
12	**1l**	2-naphthyl	Me	KOH	60	**2l**	97
13	**1m**	Ph	Me	$CsOH{\cdot}H_2O$[b]	20	**2m**	89
14	**1n**	Ph	Ph	$CsOH{\cdot}H_2O$[b]	120	**2n**	93
15	**1o**	cyclohexanone		KOH	20	**2o**	72

[a] Isolated yield by silica-gel column chromatography. [b] $CsOH{\cdot}H_2O$ (0.1 equiv) was used.

our expectations (run 9). We then examined the effect of a variety of inorganic hydroxides as catalysts for the trifluoromethylation reaction of **1a** with Me_3SiCF_3. Common bases, such as KOH and $CsOH{\cdot}H_2O$ were equally very effective as an initiator, affording the CF_3 adduct **2a** in excellent yields within 10–20 min (runs 10–12). Caesium fluoride (CsF) was also found to be efficient for this transformation to furnish **2a** quantitatively (run 13). In a slightly large-scale preparation, the product was isolated by filtration and distillation without using any solvent to give **2a** in 99.5% yield while recovering Solkane® 365mfc at 89% yield (run 14).

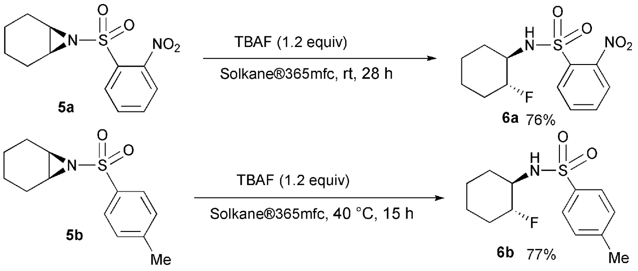
We then applied these conditions to the trifluoromethylation of a number of aldehydes (**1b–k**), and ketones (**1l–o**) to assess the potential scope and limitations of the method. The best results are summarized in Table 2. Aryl aldehydes, such as sterically demanding 1-naphthaldehyde (**1b**), conventional benzaldehyde, tolylaldehyde, *o*, *m*, or *p*-methoxybenzaldehyde, reacted in high yields (entries 2–7, 80–94%). Entries 8–9 further demonstrated that the present conditions tolerated functional groups on the aromatics, such as bromo and nitro groups. Selective 1,2-addition was observed in the reaction of cinnamyl aldehyde (**1j**) with Me_3SiCF_3 to furnish the trimethylsilyl ether of allyl alcohol **2j** in high yield (84%, entry 10). The reactions involving enolizable aldehydes posed some additional challenges due to the possibility of proton abstraction by the hard anion. As shown in entry 11, the enolizable phenethyl aldehyde (**1k**) was nicely converted to the corresponding α-trifluoromethylalcohol **2k** in 82% yield under the CsF condition. Ketones (**1l–o**) also reacted nicely under similar conditions described above in good to high yields (entries 12–15).

Next, trifluoromethylation of L-phenylalanine-derived oxazolidin-5-one **3** with Me_3SiCF_3 in Solkane® 365mfc to adduct **4** was examined. Adduct **4** is an intermediate for the synthesis of protease inhibitors. In a previous report, when oxazolidin-5-one **3** was treated with Me_3SiCF_3 and catalytic amounts of TBAF in THF, the adduct was obtained in moderate yield, and replacement of TBAF with CsF and sonication resulted in a substantial improvement of the yield (95%).[17] In Solkane® 365mfc, the reaction also proceeded quite nicely in the presence of CsF without sonication to afford **4** in 97% yield (Scheme 2).



Scheme 2 Trifluoromthylation of oxazolidin-5-one **3** with Me_3SiCF_3 in Solkane® 365mfc.

Finally, nucleophilic ring-opening fluorination of aziridines[18] with TBAF in Solkane® 365mfc was briefly examined. The reaction proceeded quite smoothly despite substitution of the arylsulfonyl group (Scheme 3). Our results are comparable to those previously reported on nucleophilic ring-opening fluorination of aziridines in an ionic liquid.[19]



Scheme 3 Nucleophilic ring-opening fluorination of aziridines with TBAF in Solkane® 365mfc.

In conclusion, Solkane® 365mfc is introduced as a novel and environmentally benign alternative solvent for the nucleophilic trifluoromethylation of aldehydes, ketones and oxazolidinone in the presence of inorganic bases. Solvolysis of Me_3SiCF_3 by Solkane® 365mfc *via* fluorophilic attraction might be responsible for this efficient transformation. It is highly advantageous that no environmentally harmful solvents, such as chlorinated alkanes or DMF, are required in any of the processes and the products, catalysts and Solkane® 365mfc are readily isolated, removed and recovered by simple filtration and distillation, respectively. This is the first example of the use of Solkane® 365mfc as a medium in an organic reaction. We believe that Solkane® 365mfc will be a green halogenated solvent for industrial use.[16] Synthetic utility of this solvent will be further demonstrated by organic reactions with non-fluorinated reagents.

Acknowledgements

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