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Trifluoromethylation of Heterocycles in Water at Room Temperature

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Abstract

Using a reaction medium containing nanoparticles consisting of commercially available TPGS-750-M in water, a combination of Langlois' reagent and *t*-BuOOH can be used to effect trifluoromethylation of several heterocyclic arrays, including heteroaromatics. These reactions take place at ambient temperatures, and the aqueous medium can be recycled.

Introduction of the trifluoromethyl group onto heterocyclic rings can often impart several desirable features associated with physiologically active compounds (e.g., increased bioavailability, membrane and metabolic stability, etc.).^{1,2} Indeed, many of the top-selling drugs contain fluorine.¹ Although there is a rich history to this area of medicinal chemistry, e.g., using CF₃Br or more commonly CF₃I³ as precursors to CF₃ radicals, opportunities remain not only for improvements in existing technologies and development of new reagents, but also for new processes that are more environmentally benign. Most recent methods rely on transition metal-mediated C-CF₃ bond constructions, and while these typically offer good control of regiochemistry, yields tend to be variable. Moreover, while processes catalytic in transition metals are known (e.g., Cu(SO₃CF₃)₂/*t*-BuOOH, L_nPd/ TESCF₃ or TMSCF₃^{4,5,6,7,8}, RuCl₂(PPh₃)₃/CF₃SO₂Cl^{9,10}, ReO₃Me/Togni reagent^{11,12}, Ru(phen)₃Cl₂/CF₃SO₂Cl, *hν*)¹³, several of the most recent procedures rely on (super)stoichiometric quantities of transition metal complexes (e.g., (MeCN)₄CuPF₆¹⁴, CuCF₃^{15,16}, CuX/TMS-CF₃^{17,18}, AgX TMSCF₃ or CF₃I¹⁹, AgNO₃/NaSO₂CF₃²⁰), which may well present limitations in terms of both waste disposal and cost.^{14,16}

Notably, every method for trifluoromethylation reported to date has been developed without attention to its environmental impact. That is, virtually no consideration has been given to the twelve guiding principles of green chemistry²¹ insofar as these reactions being done (a) in green solvents; (b) with solvent recycling, and (c) minimization of organic and/or aqueous waste being generated. In this report we describe a procedure for trifluoromethylation of heterocycles under very mild and environmentally benign conditions: in water only, and at ambient temperatures.

We focused on trifluoromethylation that relies on substitution at a C-H rather than C-X bond, thereby avoiding pre-functionalization of the educt. For this approach, the impressive method reported by Baran²² involving CF₃ radicals seemed especially attractive, utilizing commercially available Langlois' reagent (NaSO₂CF₃) as the source of these radicals. That no transition metal is needed is another positive feature. Our goal thus became one of finding conditions that would (1) eliminate use of a mixed aqueous solvent system that included a chlorinated solvent (DCM); (2) reducing the amounts of reagents involved; (3) improve yields; (4) be amenable to recycling of the purely aqueous reaction medium, and (5) reduce the level of organic waste being created, which is mainly organic solvent in nature, manifested by reduction in the associated E Factors.^{23,24}

As a test case using aqueous micellar conditions based on our designer surfactant TPGS-750-M²⁵ (Figure 1), 4-*t*-butylpyridine (**1**) was treated sequentially with NaSO₂CF₃ and then *t*-butylhydro-peroxide (TBHP), leading to an encouraging 84% conversion to the anticipated trifluoromethylated product (**2**) after 24 hours (Scheme 1), a result that is competitive with literature results on this particular educt.²²

A screening of alternative surfactants showed that other common nonionic amphiphiles led to inferior results (Table 1). The top performing surfactant (global concentration of 0.5 M) in the conversion of **1** to **2** was TPGS-750-M (entry 1), consistent with the notion that its larger particles²⁵ (ca. 50-60 nm) provide greater amounts of lipophilic material within their inner cores, and thus, have greater binding constants for substrate and reagent(s) thereby leading to enhanced levels of conversion. The corresponding "on water" reaction, where no surfactant was present, gave the lowest level of conversion (entry 8).

The results from varying the amount of TPGS-750-M from one to five weight percent for the reaction of **1** to **2** are shown in Table 2. Both two and three weight percent afforded essentially the same extent of conversion, and hence, a two weight percent solution was used in all subsequent examples. This percentage also corresponds to that found in commercially available material (Aldrich catalog number 733857).

Several peroxide radical initiators were screened in this same model reaction (**1** to **2**), and the results are shown in Table 3. In addition to TBHP, cumene hydroperoxide (CHP) was tested, as its clogP of 2.44 is much higher than that of TBHP (1.05). From previous work we anticipated that the far greater lipophilicity of CHP would translate into a greater amount of this reagent being localized within the micellar core.²⁸ However, its high viscosity created difficulties in maintaining a smoothly stirring reaction medium, with significant clumping taking place. Neither dibenzoyl peroxide nor hydrogen peroxide gave any of the desired trifluoromethylated pyridine. Thus, the preferred peroxide was clearly TBHP, affording **2** in 88% yield.

Given that Langlois' reagent contains various amounts of trace metals,²⁰ the potential for metal salts to facilitate single electron transfer from this source of CF₃ was examined. Products **3** and **4** (Table 4) result from an investigation of zinc(II), copper(I), and nickel(II) salts (10 mol %) containing varying counterions. In all cases the isolated yields decreased.

The effects of added ligands, such as TMEDA and 1,10-phenanthroline, were also not productive, the latter amine completely inhibiting the reaction.

Based on the results from these optimization studies, the procedure that emerged involves use of Langlois' reagent in combination with TBHP, both being added sequentially to the substrate in 2 weight % TPGS-750-M at room temperature. Several heterocyclic cases were then tested in an effort to establish the scope of this new process. Many of the examples previously studied by Baran and co-workers²² were directly compared, as illustrated in Table 5. In all cases, the yields are improved, while reaction times are comparable (Table 5). The regiochemistry associated with product **7** was comparable to that seen previously (C2: C3 = 1.6: 1). Noteworthy is that these reactions were run using three equivalents of NaSO₂CF₃ and five equivalents of TBHP in all cases. By contrast, in several of the examples previously reported, twice as much of each reagent was required.

Portion-wise addition of either Langlois' reagent or TBHP over time did not improve the yield. Increasing the amounts of reagents added initially (from 3 to 5 equiv of NaSO₂CF₃, and from 5 to 8.5 equiv TBHP) led to lower yields of the desired product. Additional examples (**11**^{7,29}, **12**³⁰, **13**, and **14**²⁹) are illustrated in Figure 2.

Workup of these trifluoromethylation reactions involves addition of a minimal amount of a single organic solvent, such as EtOAc, *to the reaction vessel* in order to extract the product. The total amount of water invested in the entire process is very modest, as reactions are run at 0.5 M and no additional water need be added as part of the workup. Hence, the eventual water waste stream drops to truly minimal levels. The aqueous layer retains the surfactant and hence, the reaction mixture can be recycled. Results from a recycling study for the conversion of **1** to **2** is shown in Table 6. The drop in isolated yields associated with 4th and 5th recycle is likely due to continuous buildup of *t*-butanol in the reaction mixture, which would help solubilize the product in the aqueous layer. TLC indication of each recycle suggests that the extent of conversion is also dropping, although the later reactions are not any less clean than those done earlier in the sequence.

To assess the "greenness" of this process, an E Factor was calculated²³ based on organic solvent usage, since most organic waste from organic reactions is attributable to this reaction variable.²³ Most reactions used by the pharmaceutical industry tend to have E Factors in the 25-100 range, while the fine chemicals arena is usually in the 5-25 category.²⁴ As shown in Figure 3, trifluoromethylation reactions carried out in nanomicelles involve an E Factor of only 5-6, given the complete absence of any organic solvent in the reaction medium. An E Factor calculated on inclusion of water raises this value to only 18.2, but with a single recycle this value is cut in half, in line with our previous observations relating to cross-coupling reactions performed within these recyclable nanoreactors.²³

In conclusion, micellar catalysis has been found to be amenable to radical-based trifluoromethylation of various heterocyclic compounds. Nanoreactors composed of the designer surfactant TPGS-750-M enable these substitution reactions to be performed in water at room temperature in modest to good yields. The aqueous reaction mixtures can be recycled several times, and given the limited amounts of organic solvent needed for product

isolation, the associated E Factors imply that a considerably enhanced overall level of greenness is realized using this technology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Structure of designer surfactant TPGS-750-M

Figure 2.

^a Conditions: substrate (1 mmol); NaSO₂CF₃ (3 equiv); TBHP (5 equiv); TPGS-750-M:water (2 wt. %), ^b isolated yield ^c NMR yield.

	based on:	this work	with recycling
E Factors	total organic solvent	5.6	6.1
	aqueous media included	18.2	8.9

Figure 3.
E Factors associated with trifluoromethylations.

Scheme 1.

Initial example of trifluoromethylation in water. Reaction condition: substrate (1 mmol); NaSO_2CF_3 (3 equiv); TBHP (5 equiv); TPGS-750-M (2 wt. % in water)

Table 1Impact of the surfactant of the conversion of **1** to **2**^a

entry	surfactant ^a	conversion (%) ^b
1	TPGS-750-M ²⁵	84
2	PTS-600 ²⁶	54
3	Cremophor EL	36
4	Triton X 100	22
5	Brij-30	22
6	TPGS-1000	19
7	PQS ²⁷	18
8	none	17

^a Conditions: substrate (0.1 mmol); NaSO₂CF₃ (3 equiv); TBHP (5 equiv); surfactant:water (2% w/w),^b % conversion, by GC.

Table 2Impact of wt % of TPGS-750-M on the conversion of **1** to **2**^a

entry	weight (%)	conversion (%) ^b
1	1	37
2	2	80
3	3	83
4	5	60

^a Conditions: substrate (0.1 mmol); NaSO₂CF₃ (3 equiv); TBHP (5 equiv); TPGS-750-M:Water (2 wt. %),^b % conversion, by GC.

Table 3Screening of the peroxide for the conversion of **1** to **2**^a

entry	peroxide	yield(%)
1	TBHP	88
2	CHP	72
3	Bz ₂ O ₂	0
4	H ₂ O ₂	0

^aConditions: substrate (0.1 mmol); NaSO₂CF₃ (3 equiv); peroxide (5 equiv); TPGS-750-M:Water (2 wt. %).

Table 4Effects of metal salts on the yields of the annulated pyridine **3** and substituted indole **4**.^a

		3 (C2 : C3 = 1 : 3.8)		4	
		yield (%)			
entry	metal	3	4		
1	none	73	64		
2	ZnCl ₂ ^b	51	42		
3	ZnCl ₂ ^c	0	0		
4	CuI	53	49		
5	CuOAc	54	50		
6	CuBr-SMe ₂	52	47		
7	NiCl ₂	42	ND ^d		
8	NiI ₂ (PPh ₃) ₂	47	ND ^d		
9	Ni(COD) ₂	45	ND ^d		

^a Conditions: substrate (0.15 mmol); metal salts (10 mol %) NaSO₂CF₃ (3 equiv); TBHP (5 equiv); TPGS-750-M:water (2 wt. %),^b TMEDA (1 equiv),^c 1,10-Phen (1 equiv),^d Not Determined.

Table 5

Direct comparisons with literature ²² examples

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This Work ^a				Previous Work	
entry	compound	yield (%) ^b	time (h)	yield (%) ^b	time (h)
1	3	73	43	43 ^c	40
2	4	64	44	51	18
3	5	62	28	57	24
4	6	84	23	78	40
5	7	55	44	48 ^c	40
6	8	54	51	50 ^c	40
7	9	43	38	33 ^c	48
8	10	47	52	43	61

^a Conditions: substrate (1 mmol); NaSO₂CF₃ (3 equiv); TBHP (5 equiv); TPGS-750-M:water (2 wt. %),^b See ref. 20. ^c Required second addition of reagents.

Table 6Recycling of the aqueous reaction mixture (**1** to **2**)^a

entry	cycle	yield(%)
1	1	78
2	2 ^b	79
3	3 ^b	73
4	4 ^b	68
5	5 ^b	62

^a Conditions: substrate (1 mmol); NaSO₂CF₃ (3 equiv); TBHP (5 equiv); TPGS-750-M:water (2 wt. %),^b Extracted with EtOAc; aqueous medium used for next reaction.