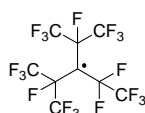


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Perfluoro-3-ethyl-2,4-dimethyl-3-pentyl Persistent Radical (Ono-Ameduri-Soloshonok Reagent): A Novel Multidimensional Reagent for Direct, Metal-Free Radical Trifluoromethylation and Polymer Initiation

CAS Registry Number: 93683-27-3



Ono-Ameduri-Soloshonok Reagent

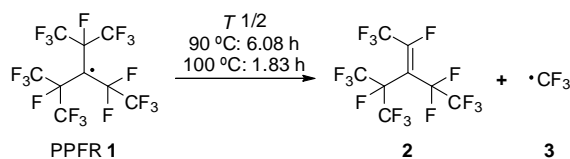
Direct, metal-free trifluoromethylation:

Fluorine-containing compounds constitute the most fast growing sector of pharmaceutical and agrochemical industries. Thus, the recent decade has witnessed an unprecedented 20% growth in the number of marketed fluorine-containing drugs [1]. Considering that the structural features of newly launched fluorine-containing pharmaceuticals clearly follow some major advances in fluorine chemistry, the development of new methods for preparation of fluoroorganic compounds as well as discovery of new fluorinated structural units, play a paramount role in shaping up the future generations of more potent and selective drugs [2]. In particular, the interest in development of trifluoromethylation methods is at all-time high [3] due to the well-established fact that CF_3 -containing drugs usually show improved efficacy, enhanced membrane permeability and, most importantly, significantly higher stability towards oxidative degradation [4].

As a result of the quite intense research activity in the area of trifluoromethylation, and in particular the radical-based methods, all available sources of trifluoromethyl radical have been already completely exhausted. Consequently, the current research is being focused on refining the reaction conditions, new substrates search and chemo/regio-selectivity. Therefore, the discovery and introduction of new reagents capable of generating CF_3 radical might be of significant scientific and methodological importance.

Just recently, the international group, led by Prof. Soloshonok (University of Basque Country), in collaboration with Dr Ono of NIAIST, Japan, has introduced a novel reagent capable of generating CF_3 radical under controlled, metal free conditions (Scheme 1) [5].

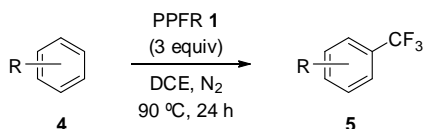
Scheme 1. Generation of CF₃ radical.



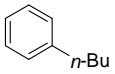
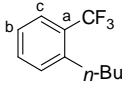
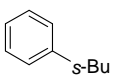
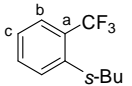
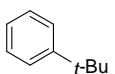
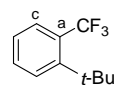

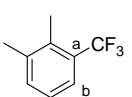

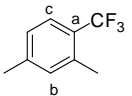

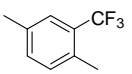
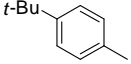
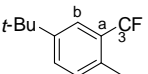

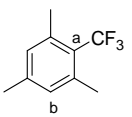

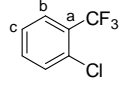

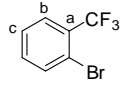
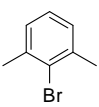
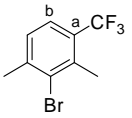
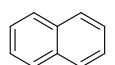
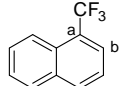
Persistent perfluoroalkyl radical PPFR **1** was synthesized in 1985 [6] by fluorination (F₂) of perfluoropropylene trimer. This procedure can be readily reproduced on a kilogram scale in good yields (up to ca. 90%) rendering compound **1** quite available on large scale, in particular considering industrial production of the starting hexafluoropropene trimer and fluorine gas. PPFR **1** is stable at ambient temperature in the open air and totally inert to the dimerization, reactions with O₂, halogens, aqueous acid or base. On the other hand, at 80-120 °C it undergoes β-scission releasing CF₃ radical **3** and totally chemically inert olefin **2** (Scheme 1).

Using these properties of PPFR **1**, Soloshonok et al. has demonstrated that various simple aromatic substrates can be efficiently trifluoromethylated thus establishing synthetic value of this new reagent. Table 1 summarize the results; in parenthesis are given yields and isomer ratios obtained by using conventional CF₃ radical reagents.

Table 1 Substrate scope of radical trifluoromethylation reaction using reagent **1**.



Entry	Substrate	Major product	Yield (%)	Isomer ratio
1 (a)			94 (81)	3.0/1.5/1.0 (2.7/1.4/1.0)(a/b/c)
2 (b)			93 (87) (81) ¹	
3 (c)			73	4.2/3.1/1.0 (a/b/c)
4 (d)			80	1.7/1.6/1.0 (a/b/c)
5 (e)			84	1.7/1.0/1.0 (a/b/c)

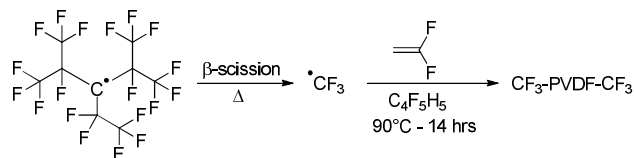
6 (f)			86	1.8/1.6/1.0 (a/b/c)
7 (g)			86	2.5/1.5/1.0 (a/b/c)
8 (h)			83	1.7/1.0 (a/b)
9 (i)			82 (65) (72)	1.3/1.0 (1.4/1.0)(2.0/1.0)(a/b)
10 (j)			75 (76) (77)	4.2/3.1/1.0 (5.2/3.5/1.0) (2.0/1.0/0) (a/b/c)
11 (k)			82 (76) ^l (77)	
12 (l)			93 (78)	2.9/1.0 (5.0/1.0) ^l (a/b)
13 (m) ^{el}			94 (78) (70) (94)	2.8/1.0 (1.0/0)(1.0/0)(1.0/2.6)(a/ab)
14 (n)			52	2.0/1.8/1.0 (a/b/c)
15 (o)			57	1.5/1.3/1.0 (a/b/c)
16 (p)			89 (75)	3.2/1.0 (4.0/1.0)(a/b)
17 (q)			84 (70)	6.8/1.0 (4.8/1.0) (a/b)

Considering the data presented in Table 1, one may agree that the use of the benchtop stable PPF_R **1** as trifluoromethylation reagent features several benefits, including controllable rate of CF₃ radical release, totally metal-free one-step process under operationally convenient conditions, which, most likely, bodes well for PPF_R **1** widespread, general application.

Polymer Initiation:

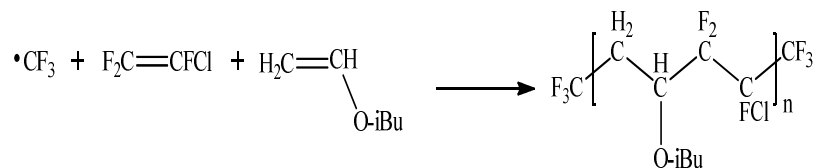
Fluorinated polymers are quite exceptional, niche macromolecules that play an integral role in modern life [7]. They range from semi-crystalline to fully amorphous, and their uses span engineering thermoplastics and elastomers for the automotive and aeronautics industries, weather-proof coatings, biomedical materials, membranes for use in Li-batteries and fuel cells, and many more [8,9]. Fluoropolymers possess extraordinary physical and chemical properties, *viz.* high chemical-, thermal-, aging-, and weather resistance, as well as outstanding inertness to hydrocarbons, acids, and bases. Other highly desirable properties include low dielectric constant, low surface energy (water and oil repellency), low flammability, low refractive index, and low moisture absorption. Furthermore, the high strength of the C–F bond ($485 \text{ kJ}\cdot\text{mol}^{-1}$) grant fluoropolymers unparalleled resistance to oxidation [10-14].

One of the main challenges lies in the assessment of the molecular weights of Fluoropolymers. They are difficult to estimate and usually these values are supplied in PMMA (or polystyrene) equivalents. This does not allow reporting “true” MW values. Recently, Ameduri’s group has been able to synthesize original CF_3 -PVDF- CF_3 from the radical polymerization of vinylidene fluoride (VDF) initiated from a $^\circ\text{CF}_3$ radical released from the PPRF persistent radical [15] (Scheme 2).



Scheme 2. Radical polymerization of vinylidene fluoride (VDF) initiated from a CF_3 radical released from perfluoro-3-ethyl-2,4-dimethyl-3-pentyle PPRF persistent radical [15].

That strategy was also successfully applied in copolymerization of VDF with 7 fluorinated comonomers [16,17] or more recently in radical copolymerization of chlorotrifluoroethylene (CTFE) with vinyl ether [18] (Scheme 3).



Scheme 3. Radical copolymerization of chlorotrifluoroethylene (CTFE) with isobutyl vinyl ether initiated from a CF_3 radical released from perfluoro-3-ethyl-2,4-dimethyl-3-pentyle PPRF persistent radical **1** [18].

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