



Co-thermolysis: a one-pot synthetic method for novel 2-substituted-5-(trifluoromethoxy)thiophenes

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ABSTRACT

A new 'green' process to obtain trifluoromethoxylated compounds by a gas-phase method has been accomplished. Through it, new 2-substituted-5-(trifluoromethoxy)thiophenes have been obtained in moderate to good yields. Though the reaction occurs in the gas-phase and radicals are involved, an electron transfer mechanism is also postulated to explain the appearance of all detected products.

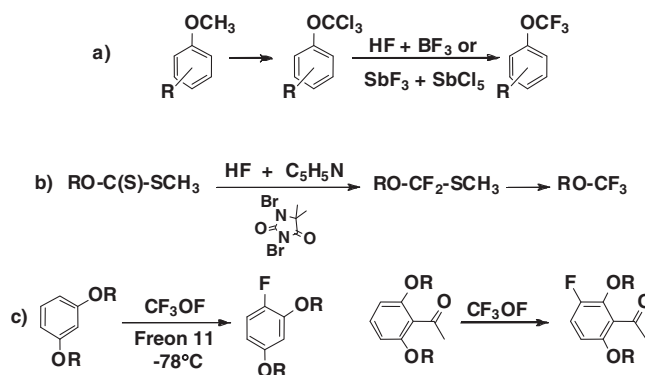
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Organic fluorine compounds often show unusual properties and behavior in comparison with non-fluorinated parent compounds.¹ The introduction of fluoroalkyl groups is not an easy task, since the usual methods for alkylation cannot be applied due to the high electronegativity of the fluorinated group. Especially, an exploration of electrophilic perfluoroalkylating and perfluoromethoxylating agents is desired since reactions involving a perfluoroalkylation as an intermediate are very limited.²

The chlorination/exchange sequence is routinely used for the preparation of trifluoromethoxy-substituted arenes. The displacement of the heavier halogen (Cl) by the lighter one (F) can be brought about with anhydrous hydrogen fluoride in the presence of a catalytic amount of boron trifluoride or with antimony trifluoride in the presence of antimony pentachloride (Scheme 1a)^{3,4} and is compatible with substrates carrying electron-withdrawing groups. The trifluoromethoxy arenes are obtained in yields ranging from 9% to 80%. Other method has been disclosed, when dithiocarbonates (xanthogenates) are exposed to a huge excess of hydrogen fluoride–pyridine and 1,3-dibromo-5,5-dimethylhydantoin, Scheme 1b.^{5,6}

Reagents containing fluorine bonded to a heteroatom (X–F) are highly reactive because of the lone pair electron repulsion between them; for that reason, they have been employed effectively to introduce either X or F to target molecules. The relative electron-withdrawing nature of X compared to F will determine which one will be the reactant group. Typical fluorine-activated electrophilic reagents are F–Cl, F–Br, F–I, and F–PhSe. On the other hand, reactants that yield F-derivatives (electrophilic fluorinating reagents) are F–F, AcO–F, CF₃CO₂–F, R₃N⁺–F, and Py⁺–F.

The electrophilic addition of CF₃OF to aromatic compounds has been found to produce mono-fluorinated compounds instead of trifluoromethoxylated derivatives.



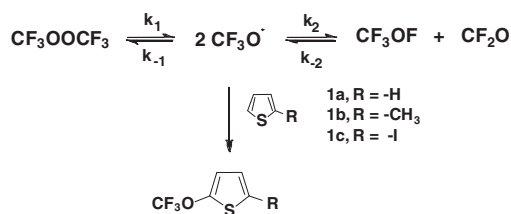
Scheme 1. Synthesis of trifluoromethyl aryl/alkyl ethers and fluorinated aromatics rings.

The reaction goes through the attack of the fluorine atom to the aromatic ring through a typical electrophilic aromatic substitution, Scheme 1c. This behavior is attributable to the strong electron-withdrawing capacity of the trifluoromethoxy group which is, together with the FCO group, one of the very few moieties with more electron-withdrawing capacity than the F atom.⁷

In this work, we present the direct synthesis of 2-substituted-5-(trifluoromethoxy)thiophenes by a co-thermolysis between bistrifluoromethyl peroxide CF₃OOCF₃ (BTMP, 2) and 2-substituted-thiophenes. The pyrolysis of bistrifluoromethyl peroxide is a complex reaction initiated by CF₃O radicals. Descamps and Forst⁸ reported that the overall rate constant involves at least three different reaction steps, which are the initial fragmentation of BTMP into two radicals, their recombination, and the disproportionation to CF₂O and CF₃OF, Scheme 2.

Therefore, the purpose of this work is to scavenge CF₃O radicals with 2-substituted thiophenes, in order not to measure the kinetics but to explore new synthetic ways to obtain perfluoromethoxylated

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Scheme 2. Scavenge of CF_3O radicals by co-thermolysis with thiophenes.

ed compounds in a direct one-pot gas-phase reaction, as opposed to the many steps and reagents required in the reactions shown in Scheme 1a and b that have been the benchmarks for CF_3O radical insertion.

Co-thermolysis has been performed by heating the mixture of BTMP **2** (CF_3OOCF_3) and the corresponding 2-substituted thiophenes (**1a–c**) at 200 °C. The reactions were performed at this temperature because both reactants are in gas-phase; we previously verified that compounds **1a–c** stay unreacted at these conditions. It is well known that the symmetric peroxide decomposes slowly in CF_3O radicals under heating.⁹ Nevertheless, when we carry out the reactions, a pronounced acceleration was observed in the decomposition of **2**. Thus, 2-substituted-5-trifluoromethoxy-thiophenes were obtained in 10–67% yields as revealed by GC/MS analyses carried out on the crude of the reactions after appropriate solvent extraction.¹⁰

Particularly, the co-thermolysis reaction of thiophene **1a** and 2-methyl-thiophene **1b** yielded some undesired amounts of polymers as well as other compounds, besides the trifluoromethoxy-thiophenes **3a,b** (in 9% and 22% yields, respectively). There is also an increase in the concentration of products with time. In fact,

for compound **3a**, its concentration doubles at 15 min, as should be expected for a simple reaction. Nevertheless, the increase in polymeric products is even greater, suggesting that they come from the decomposition of **6** which is unstable at the reaction temperature, (Table 1 and Scheme 3).

In the case of 2-iodo-thiophene **1c**, the reaction yields even more interesting compounds depending on the reaction time.

At short reaction times, the main products are the corresponding trifluoromethoxy-thiophene **3c** and 2,5-di-iodo-thiophene **11**, (Table 1 and Scheme 4).

In order to verify that compound **11** is formed as a consequence of **2** being present in the reaction, compound **1c** was reacted with and without iodine at 200 °C. In both cases only the unreacted material was recovered, meaning that the formation of **11** occurs only in the presence of bistrifluoromethyl peroxide **2** and that this reaction competes with the formation of **3c**.

All the reactions were performed with a 1:1 ratio of reagents except the very last one. After 15 min, nearly 10% of 2-iodo-thiophene **1c** was recovered. The main products were 2-iodo-trifluoromethoxy-thiophene **3c** and di-iodo-thiophene **11**. The quantity of **11** is almost the same as that at 10 min of reaction; but after 20 min, **11** goes down in concentration, while **3c** increases (though the amount of remaining reagent **1c** is very low). Therefore, we propose that **11** is reacting to afford **3c**, as Figure 1 shows through the increase in slope for its production after around 15 min.

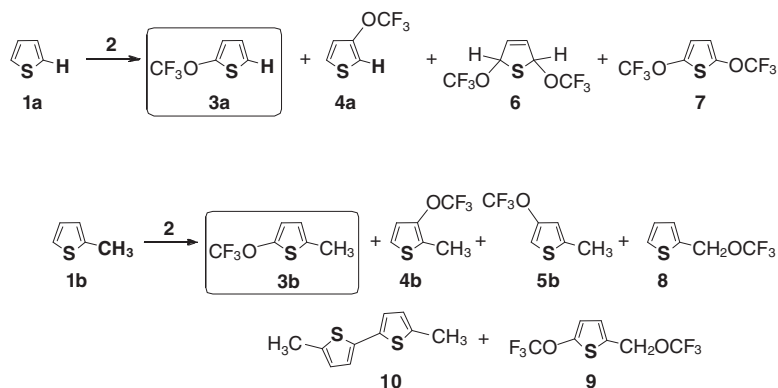
Other interesting products start to appear, though in low yield, after 15 min of reaction. Compounds **12** and **13** would be formed through the same mechanism as for **11**, and could be responsible for the generation of **15** and **16**. Besides, **14** affords a mixture of **17** and **18**.

The possible reaction mechanisms for the synthesis of the main products are given in Scheme 5a. The path labeled **A** suggests a

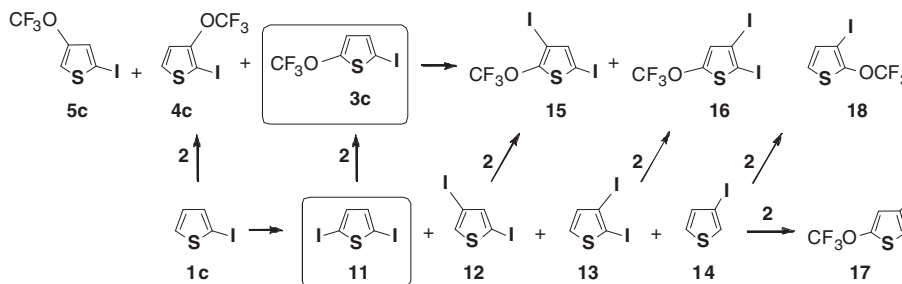
Table 1
Reaction of thiophenes **1a–c** with bistrifluoromethyl peroxide (BTMP) at 200 °C

Compd	Time (min)	Percentages obtained in the gas-phase reaction														
		1	3	4,5	6	7	8	9	10	11	12	13	14	15	16	17,18
a, H	5	95.1	4.3	—	0.6	—	—	—	—	—	—	—	—	—	—	—
	15	—	9.1	0.3	0.4	0.2	—	—	—	—	—	—	—	—	—	—
b, CH₃	10	66.4	21.5	1.3	—	—	9.5	0.4	0.9	—	—	—	—	—	—	—
	5	85.9	5.3	0.4	—	—	—	—	—	8.4	—	—	—	—	—	—
c, I	10	56.7	19.8	1.4	—	—	—	—	—	22.0	—	—	—	—	—	—
	15	7.1	37.7	3.5	—	—	—	—	—	21.9	4.0	10.2	4.0	3.5	3.2	5.0
	20	1.7	67.3	2.9	—	—	—	—	—	6.3	2.9	3.0	0.4	8.4	5.2	2.4
	15*	46.7	15.7	1.2	—	—	—	—	—	35.1	—	0.6	0.7	—	—	—

* Ratio of reactants **1c** to **2** 1:0.5.



Scheme 3. Reaction of thiophene **1a,b** with BTMP **2** at 200 °C.



Scheme 4. Synthesis of trifluoromethoxy iodo thiophenes by co-thermolysis of **1c** with BTMP **2**.

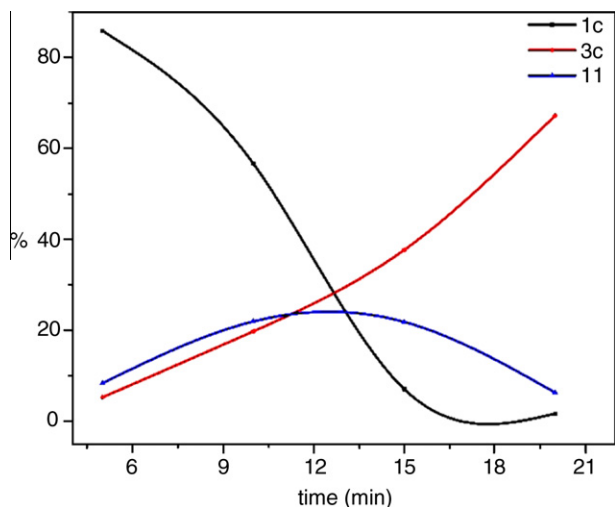


Figure 1. Relative concentration of compounds **1c**, **3c**, and **11** against time at 200 °C.

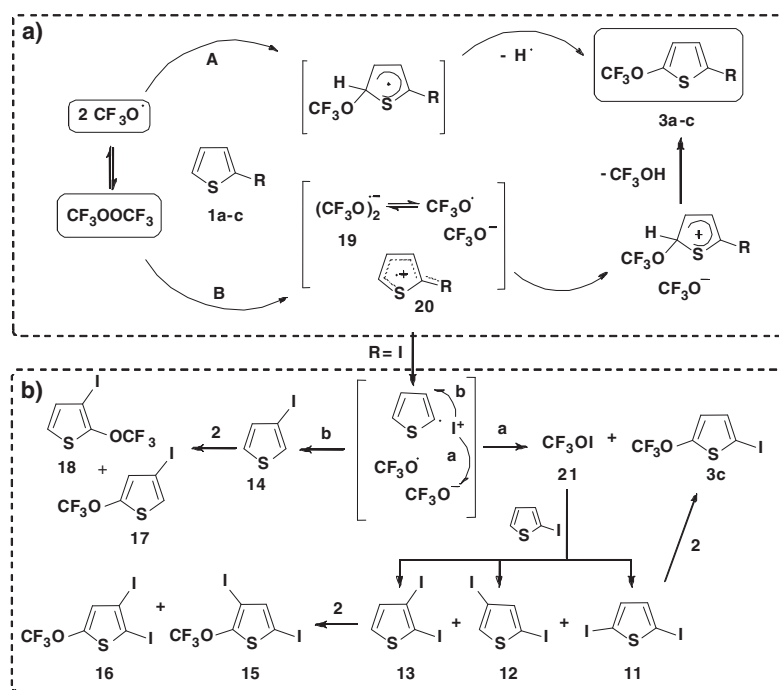
free-radical character for this reaction, initiated by the attack of the CF_3O radicals on 2-substituted thiophenes as expected. Nevertheless, another path could be postulated (**B**).

Mechanism **B** is an electron transfer process from the substrate to peroxide **2** to give a radical cation and a radical anion (**19**), which decompose into trifluoromethoxyl radical and trifluoromethanolate, respectively. The trifluoromethoxyl radical should recombine with the heterocyclic-radical cation to give trifluoromethoxylated compounds, as shown in Scheme 5. However, this path could be thermodynamically unfavorable, because the reactions are carried out in gas-phase. Nevertheless, gas-phase acylation of simple five-membered heteroarenes¹² and reactions of some peroxides with thiophene and furan via an electron transfer process where acceleration was observed have been reported.^{13,14}

MO calculations showed that the higher the electron-withdrawing ability of the substituent, the lower the O–O antibonding energy level. Thus, the electron transfer (ET) should occur faster.¹² In our case, due to the high electron-withdrawing ability of the trifluoromethoxyl group, the ET process should be fast and the reaction through path **B** should predominate over path **A**.

In addition, path **B** could explain the regioselectivity in the formation of the main products; while in a free-radical reaction a low regioselectivity is expected.¹³

On the other hand, if the reaction proceeds through a free-radical process, the rate-determining step should be the fragmentation of peroxide **2** in two CF_3O radicals and its rate should not be accelerated by the presence of thiophenes. In fact, the rate of decomposition was accelerated by around one order of magnitude, as it can be seen in Figure 2.



Scheme 5. Reaction mechanisms for the trifluoromethoxylation of thiophenes. The lower part applies only to **1c**.

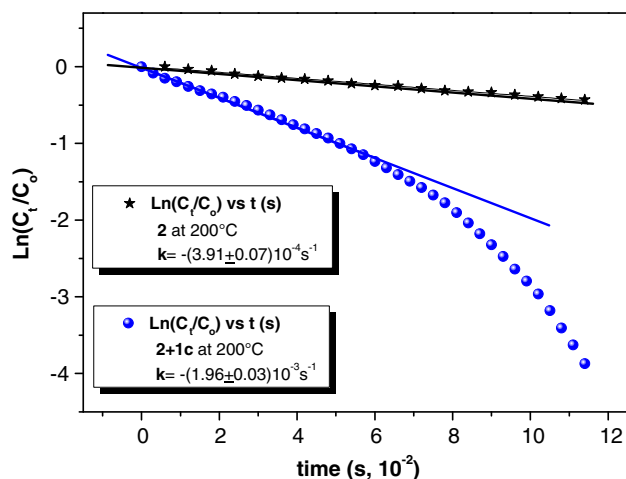


Figure 2. Temporal variation of concentration of **2** both in the absence and in the presence of **1c** as seen through gas-phase IR spectroscopy.¹¹

Conclusive evidence in favor of path **B** is the experimental run shown in the last row of Table 1. With a reagent's ratio (**1c** to **2**) of 1:0.5, the starting material was recovered in amounts of 47%, in contrast to the observed 7% for a 1:1 ratio. This can be rationalized only if the reaction proceeds through this particular process with the CF₃O radical being formed from the radical anion **19**, which is not equimolar to **1c**. The trifluoromethanolate anion immediately abstracts the H atom forming CF₃OH and the system recovers aromaticity. The CF₃OH was not detected due to its fast decomposition into CF₂O and HF, both of them experimentally detected in the reaction mixture. Had the reaction occurred exclusively through path **A**, the CF₃O radicals would equal the amount of **1c** molecules; thus, they should have reacted completely, giving products **3**, **4**, and **5** with a low regioselectivity.

In order to explain the other compounds obtained from **1c**, on the basis of an ET mechanism, we propose that the counterpart of **19**, that is, the radical cation **20** decomposes into thienyl radical and iodine cation, Scheme 5b. Recombinations of these species afford CF₃OI (**21**), **3c**, and **14**. The CF₃OI is a powerful electrophilic species, like CF₃OF,⁷ and reacts with the available **1c** to give **11**, **12**, and **13**, through an electrophilic aromatic substitution. These diiodinated derivatives react with **2** to yield the other fluorinated compounds.

In summary, we have been able to show that the gas-phase reaction of fluorinated peroxides opens new synthetic paths to the attainment of products that are either difficult to obtain through more conventional and cumbersome fluorination methods or completely new. There is, of course, a need for rigorous and detailed study of the many possibilities about changing the reaction's conditions to improve the selectivity as well as the yield of the desired products.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures and CG–MS characterization of all compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.111.

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