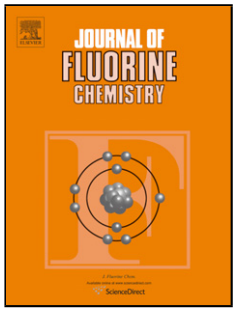

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Reaction of CF_3-ynones with methyl thioglycolate. Regioselective synthesis of 3-CF_3-thiophene derivatives

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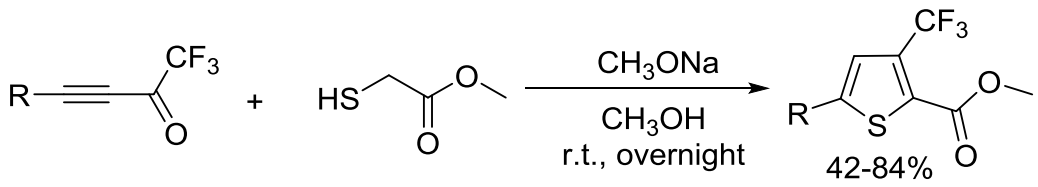
Graphical abstract



Highlights

- Efficient synthesis of 3-CF3-thiophene derivatives has the following merits:
- -the method is regioselective
- - the method is general to open access to 5-aryl and 5-alkyl substituted derivatives
- -the reaction proceeds under room temperature to give target compounds in up to 84% yields

Abstract*: Efficient regioselective synthesis of 3-CF_3-substituted thiophene derivatives was elaborated using addition of methyl thioglycolate to CF_3-ynones in the presence of sodium methoxide.*

Keywords: fluorine; trifluoromethyl group; thiophene; Michael addition; regioselectivity

1. Introduction

Thiophene is one of the most important aromatic heterocyclic derivatives. A lot of thiophene derivatives demonstrated practical application. For example, thiophene is important pharmacophoric unit and many drugs incorporate this heterocyclic core in the structure. Such thiophene derived drugs as Spiriva, Xarelto, Plavix and Invokana have over one billion annual sales (Figure 1).1 Moreover, thiophene derivatives have found broad application in material science.2

Nowadays, growing interest to thiophenes having fluorine atom or perfluorinated substituents in the structure is observed. This family of thiophenes is intensively studied as perspective type of soluble semiconductors, polymers, blue light emitting materials, and liquid crystals.3 Thiophene derived perfluorinated cyclopentenes have been studied as thermally irreversible photochromic compounds with high resistance to fatigue.4 Moreover, some fluorinated thiophenes demonstrated attractive biological activity.5 However, fluorinated thiophenes are still rare type of molecules which is difficult to synthesize.6 Some examples of trifluoromethylated thiophenes condensed with other heterocycles as well as tetrahydro-derivatives can be found in the literature.7

This study is devoted to systematic investigation of the reaction of acetylenic CF_3-ketones **1** with methyl thioglycolate to open access to family of thiophenes bearing a CF_3-group at the beta-position. We found in the literature the only example of similar approach with CF_3-acetylenic ketone having acetal fragment at the triple bond.8 Similar synthesis of thiophenes from non-fluorinated ynones has been described recently by Müller.9 However, no data about reactivity of aryl substituted CF_3-ynones can be found in literature. Moreover, we investigated the reaction of methyl thioglycolate with the corresponding dibromoenone10 prepared by addition of bromine to CF_3-ynone **1a** to open access to 3-CF_3-thiophene derivative having additional bromine atom in the position 4.

2. Results and discussion