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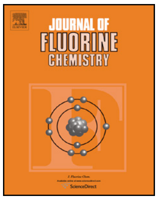

# Substituted 4-(*1H*-1,2,3-triazol-1-yl)-tetrafluorobenzoates: Selective synthesis and structure

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ABSTRACT

Regioselective, simple and fast synthesis of a series of [2 + 3]-cycloaddition products, **2-11**, 4-(4-$RC_2HN_3$)$C_6F_4CO_2Et$ (**2**: R = Ph; **3**: R = $CMe_2OH$; **4**: R = $CH_2OH$; **5**: R = $CO_2Et$; **6**: R = *n*-$C_5H_{11}$; **7**: R = $CH_2O$-*o*-$C_6H_4CHO$; **8**: R = $CH_2O$-*p*-$C_6H_4NHBoc$; **9**: R = $CH_2O$-*p*-$C_6H_4CH_2OH$; **10**: R = $CH_2O_2CC_6F_5$; **11**: R = *p*-$C_6H_4Bu$-*t*), in reaction between ethyl 4-azido-2,3,5,6-tetrafluorobenzoate, **1**, and a number of substituted alkynes was elaborated under conditions of copper-catalyzed click chemistry reaction. The optimized conditions include application of CuBr and $Et_3N$ in dichloromethane. The structure of compounds **2-11** was investigated in solution by 1D and 2D NMR and IR spectroscopy. The molecular structure of **2** in solid state was established by X-ray analysis.

## 1. Introduction

Fluorine containing benzoic acids and benzoates are sharply differed on their properties from related hydrogen analogs and so nowadays found wide application for construction of new materials [1], as ligands for various metals [2], precursors for liquid crystals and luminescent materials [3], biologically active compounds [4]. Furthermore, metal perfluorobenzoates may be regarded as catalysts of different processes in organic synthesis [5].

Reaction of 1,3-dipolar cycloaddition between azides and alkynes, widely known as click chemistry reaction, is applied for synthesis of different triazoles under green chemistry conditions [6]. Substituted triazoles possess potential biological activity and may be used for medicaments elaboration against tuberculosis [7], HIV [8], and also as antiepileptic [9], anticancer [10] and antimicrobial agents [11]. The 4-aryl-1H-1,2,3-triazoles were discovered to be a unique template for the inhibition of the metalloprotease MetAP2 [12]. Furthermore, these derivatives find application as proton transfer agents [13], precursors for construction of polymer [14] or liquid crystals [15]. So a simple and efficient way of synthesis of such compounds should be developed.

It should be noted that synthesis of differently substituted triazoles containing perfluorophenyl group has been elaborated only partly. Thus substituted aryl azides with electron withdrawing group reacts in cycloaddition reactions very easily [16]. There are only several works concerning related compounds [17] and there are no well-performed [18] works concerning copper-catalyzed azide – alkyne cycloaddition (CuAAC) and especially corresponding benzoic acids. The aim of this work is a development of a method of synthesis of a wide range of substituted triazoles containing tetrafluorobenzoate fragment.

## 2. Results and discussion

In this work the synthesis of initial compounds, ethyl pentafluorobenzoate and ethyl 4-azidopentafluorobenzoate (**1**), is described. The well known synthetic procedures (carboxylic acid esterification, nucleophilic substitution in $C_6F_5$ ring) [19] were used for the synthesis of the target compounds. At the same time we worked out new approach to synthesize $C_6F_5CO_2Et$ using Grignard reagent [20] what allows to obtain esters in moderate yields (Scheme 1). The last method should be used for the synthesis of substituted perfluoroarene carboxylic acids. It was established that reverse slow addition (addition of Grignard reagent to the ethyl chloroformate at low temperature) is crucial for the successful synthesis. Even despite this the significant amount (up to 30%) of undesired by-product, $(C_6F_5)_2C{=}O$ [21], may be isolated from the reaction mixture. Besides, ethyl pentafluorobenzoate may be prepared using common method from free acid using $SOCl_2$ (Scheme 1).

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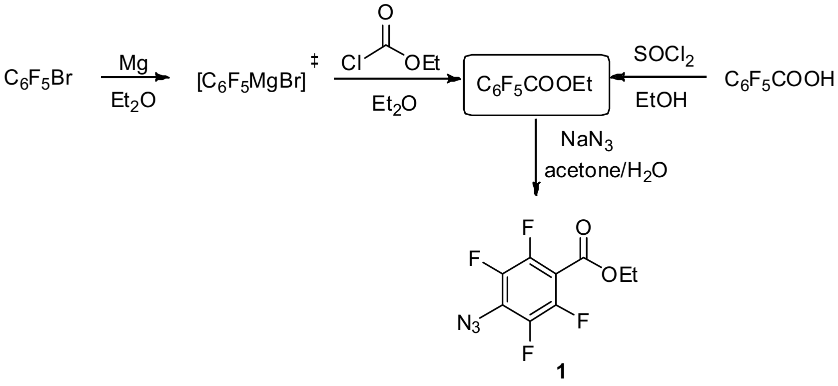


**Scheme 1.** Synthesis of $C_6F_5CO_2Et$ and 4-$N_3C_4F_4CO_2Et$ (**1**).

Compound **1** was synthesized by the selective nucleophilic aromatic substitution of a *para*-fluorine atom in ethyl pentafluorobenzoate with azide ion using known way [22]. It should be noted that two ethyl esters obtained in this work, $C_6F_5CO_2Et$ and *p*-$N_3C_6F_5CO_2Et$ (**1**), are new compounds.

The most general methodology suitable for the synthesis of 1,2,3-triazoles is the Huisgen 1,3-dipolar cycloaddition, i.e. the reaction between alkyl or aryl azides and terminal acetylenes [23]. If the cycloaddition is thermally induced, approximately equimolar mixture of the 1,4- and 1,5-regioisomers of triazole is usually obtained [24]. Various attempts to control the regioselectivity without much success were reported until the discovery of the copper(I)-catalyzed reaction, which exclusively yields the 1,4-disubstituted 1H-1,2,3-triazoles [25].

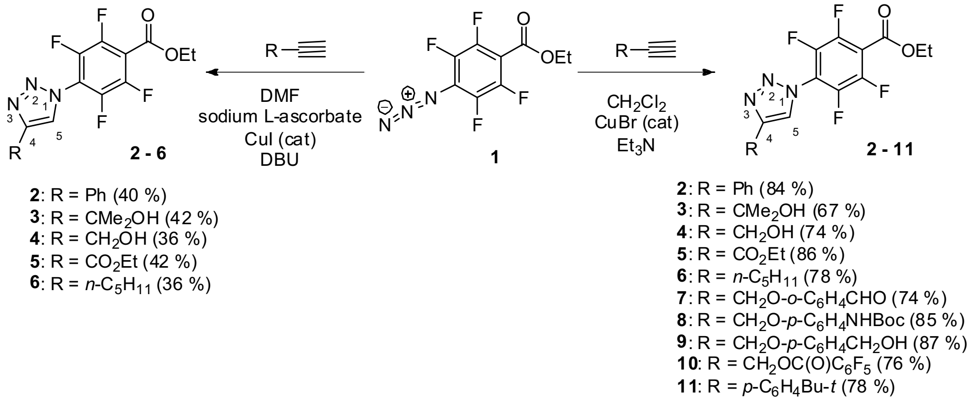
In this article a wide series of substituted triazoles was obtained containing electron donating and electron withdrawing substituents. At the first stage the known conditions for related non-fluorinated aryl azides [26] were used. The conditions of copper-catalyzed azide-alkyne cycloaddition (CuAAC) reaction have been used in this case. There were catalytic quantity of CuI (up to 20 molar%), sodium ascorbate (up to 40%) and DBU (1,8-diazabicyclo [5.4.0]undec-7-ene) as a base (up to 1 eq.) were applied (Scheme 2, Table 1). It should be noted that absence or decreasing the quantity of DBU or sodium ascorbate results in decreasing the yield of target product and appearance of significant amount of side products, for example, the products of homocoupling ($[PhCC]_2$ in the case of **2**) which may be isolated after column chromatography with preparative yield (up to 18%). The related situation is observed at decreasing the quantity of sodium ascorbate. It should be noted that increase the temperature results in partial azide reduction [27]. But anyway in this case the target compounds were isolated only in moderate yields (36 – 42%).

**Table 1**
Conditions for CuAAC in the case of ethyl 4-azido-tetraflurobenoate.

| Copper system | Base | Conversion/time[a] (yield, %) |
|---|---|---|
| CuI, sodium ascorbate, DMF | DBU | >98/2 (40) |
| CuI, sodium ascorbate, DMF | $Et_3N$ | >98/4 (44) |
| CuI, sodium ascorbate, DMF | – | traces/40 |
| CuI, DMF | DBU | 26/40 |
| CuI, DMF | $Et_3N$ | 30/40 |
| $CuSO_4$*$5H_2O$, sodium ascorbate, $H_2O$:*t*-BuOH | – | 12/40 |
| CuBr, $CH_2Cl_2$ | – | traces/40 |
| CuBr, $CH_2Cl_2$ | $Et_3N$ | >98/4 (84) |

[a] According to $^{19}F$ NMR, isolated yield in parentheses; time in hours.

So the work concerning the searching for better conditions has been done using model interaction of *p*-$N_3C_6F_4CO_2Et$ with PhC≡CH (Table 1). It should be noted that typical conditions of CuAAC reaction with $CuSO_4$*$5H_2O$ [25] gave unsatisfactory results. Changing the copper source and applying trivial base we established that using CuBr, $Et_3N$ in dichloromethane instead of CuI, DBU in DMF allows to obtain the target compounds in higher yields (up to 84%, see Table 1). Furthermore, in the last case the isolation procedure is simpler including only filtration. In the absence of the base the reaction is very slow (see Table 1). Thus the



**Scheme 2.** Synthesis of compounds **2–11**.