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Reaction of CF_3-ynones with azides. An efficient regioselective and metal-free route to 4-trifluoroacetyl-1,2,3-triazoles

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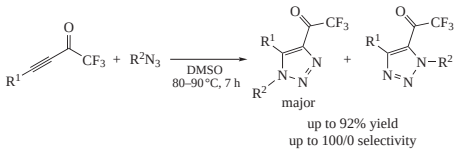
[3+2] Cycloaddition of CF_3-ynones with azides proceeds regioselectively to give 1-R-4-trifluoroacetyl-1*H*-1,2,3-triazoles as the major products.



Organofluorine compounds, in particular, those of heterocyclic family, are applied in modern medicinal chemistry.[1] Since direct fluorination is not always selective or demands expensive fluorinating reagents, the use of fluorinated building blocks is more expedient. Recently, we have demonstrated high synthetic utility of trifluoromethyl alkynyl ketones (CF_3-ynones) for the synthesis of fluorine-containing pyrazoles,[2] pyrimidines[3] and diazepines.[4] Herein, we present the efficient preparation of trifluoroacetylated 1,2,3-triazoles based on these building blocks.

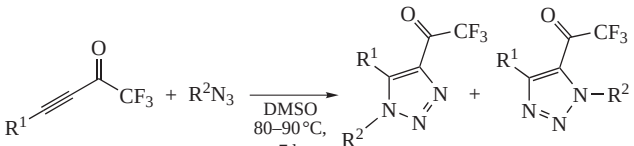
To the best of our knowledge, the only reported synthesis of trifluoroacetyltriazoles is based on the reaction of β-ethoxyvinyl trifluoromethyl ketone with aryl and benzyl azides affording regioselectively 1,4-disubstituted triazoles in good to high yields.[5] However, prolonged reaction time (24–144 h) and elevated temperature (80 °C) were needed for full conversion of the reactants. In case of enones with additional subtituents in β-position, more drastic conditions (130–150 °C) were exploited to give mixtures of regioisomeric triazoles.[6] Some examples of addition of azides to non-symmetrical acetylenic ketones can be found in literature, however all these reactions were performed using transition metal catalyst to promote cycloaddition.[7] Normally, if no catalyst is used, the Huisgen reaction affords regioisomeric triazoles starting from of non-terminal acetylenes or alkenes.[8] However, in case of substrates with strong electron-withdrawing or electron-donating groups at multiple bonds, mostly or exclusively one regioisomer is formed, *e.g.*, from 1-trifluoromethylated 1,3-dicarbonyl compounds a single 1,2,3-triazole isomer was obtained.[9]

We anticipated that polarization of the triple bond with trifluoroacetyl group should permit [3+2] cycloaddition to proceed regioselectively. The reaction of CF_3-ynone **1a** with ethyl azidoacetate was chosen as a model one (Scheme 1). It was found that the reaction proceeded on heating (80–90 °C) to form a mixture of regioisomeric triazoles **2a** and **3a**, in which one of the regioisomers is dominant. The ratio of the regioisomers depended significantly on polarity (dielectric constant) of the solvent (Table 1). Thus, in dioxane, whose dielectric constant is the smallest in the studied solvent series, the content of minor isomer **3a** is maximal and approximately equal to that of isomer **2a** (entry 1). With

Table 1 Reaction between CF_3-ynone **1a** and ethyl azidoacetate in different solvents.

Entry	Solvent	Dielectric constant	Catalyst (10 mol%)	Yield of **2a** + **3a** (%)[a]	**2a**:**3a** ratio[a]
1	Dioxane	2.30	–	84	55:45
2	Toluene	2.38	–	94	79:21
3	NEt_3	2.42	–	tarring	–
4	Neat	–	–	86	87:13
5	THF	7.50	–	93	89:11
6	EtOH	24.55	–	19	96:4
7	MeCN	37.50	–	80	96:4
8	MeCN	37.50	CuI	78	94:6
9	MeCN	37.50	$Zn(OTf)_2$	82	96:4
10	DMSO	46.70	–	92	96:4
11	DMSO	46.70	CuI	83	94:6
12	Propylene carbonate	64.00	–	87	95:5

[a] Determined by ^1H and ^{19}F NMR.



1a–j **2a–n** **3a–n**

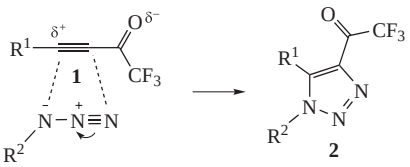
	R^1	R^2	Yield of **2** + **3** (%)	**2**:**3** ratio
a	Ph	CH_2CO_2Et	92	96:4
b	4-MeC_6H_4	CH_2CO_2Et	55	94:6
c	4-BrC_6H_4,	CH_2CO_2Et	66	98:2
d	4-ClC_6H_4	CH_2CO_2Et	46	96:4
e	4-$MeOC_6H_4$	CH_2CO_2Et	62	91:9
f	4-$MeSC_6H_4$	CH_2CO_2Et	58	98:2
g	4-$Bu^tC_6H_4$	CH_2CO_2Et	42	98:2
h	3,4-$Me_2C_6H_3$	CH_2CO_2Et	62	96:4
i	*n*-C_6H_{13}	CH_2CO_2Et	51	100:0
j	4-methoxy-1-naphthyl	CH_2CO_2Et	67	100:0
k	Ph	Bn	58	91:9
l	Ph	4-ClC_6H_4	89	80:20
m	Ph	4-$MeOC_6H_4$	89	88:12
n	Ph	4-$O_2NC_6H_4$	69	99:1

Scheme 1

increasing the solvent dielectric constant, the amount of minor isomer **2a** decreases dramatically (entries 2–5). The reaction in highly polar solvents with dielectric constant higher than 25 (ethanol, acetonitrile, DMSO, propylene carbonate, entries 6, 7, 10, 12) occurred selectively, and the amount of 1,5-isomer **3a** in these cases dropped to 4–5%. The further growth of the solvent polarity did not affect the content of the minor isomer. Also, addition of Cu or Zn catalysts did not substantially influence the ratio between isomers (entries 8, 9, 11). The best results were achieved in DMSO (entry 10).

Under optimal reaction conditions (heating in DMSO at 80–90 °C),[†] synthetic scope of the reaction was investigated (see Scheme 1). The reaction of various acetylenic ketones **1a**–**j** with ethyl azidoacetate afforded a series of trifluoroacetyltriazoles **2** in good yields. In all cases the reaction proceeded regioselectively to give 1,4-regioisomer **2** as the main product. The content of the minor isomer did not exceed 5–6%, and in the case of CF_3-ynones **1i** and **1j** bearing *n*-hexyl and naphthyl substituents, the reaction results in the exclusive formation of corresponding isomers **2i**,**j**. It should be noted that in most cases minor regioisomer can be easily removed by the column chromatography. Next, the reaction of various azides with CF_3-ynone **1a** was studied. Aryl azides bearing both electron-donating and electron-withdrawing substituents as well as benzyl azide were involved into cycloaddition to give regioselectively triazoles **2** in good to high yields (see Scheme 1).

The regiochemical result leading to 1,4-isomer is dictated by polarization pattern in the acetylene and azide moieties, namely, the β-carbon atom of the triple bond is positively charged to coordinate negatively charged nitrogen atom of the azide group (Scheme 2).



Scheme 2

[†] *Synthesis of 1,2,3-triazoles* **2**, **3** (*general procedure*). A 3 ml vial with a screw cup was charged with the corresponding azide (1.1 mmol), DMSO (2 ml, or another solvent), corresponding CF_3-ynone **1** (1 mmol) and heated at 80–90 °C for 5–7 h. The mixture was then poured into 0.1 M HCl (10 ml) and extracted with CH_2Cl_2 (3 × 10 ml). The combined extracts were dried over Na_2SO_4, the volatiles were evaporated, and the residue was purified by column chromatography on silica gel using the CH_2Cl_2–MeOH (30 : 1) mixture as an eluent.

*Ethyl (5-phenyl-4-trifluoroacetyl-1*H*-1,2,3-triazol-1-yl)acetate* **2a**. Colourless oil, yield 300 mg (92%), isolated as 96 : 4 mixture with isomeric triazole **3a**. IR (ν/cm^{-1}): 1725 ($COCF_3$), 1753 (CO_2Et). ^{1}H NMR ($CDCl_3$) δ: 1.23 (t, 3H, *Me*CH_2, *J* 7.1 Hz), 4.21 (q, 2H, Me*C*H_2, *J* 7.1 Hz), 5.05 (s, 2H, CH_2), 7.36–7.40 (m, 2H, Ph), 7.48–7.60 (m, 3H, Ph). ^{13}C NMR ($CDCl_3$) δ: 13.9, 49.2, 62.7, 116.1 (q, CF_3, *J* 290.4 Hz), 123.9, 129.1, 129.2, 131.1, 137.8, 144.8, 165.5, 174.1 (q, *C*OCF_3, *J* 37.6 Hz). ^{19}F NMR ($CDCl_3$) δ: –75.3. *Ethyl (4-phenyl-5-trifluoroacetyl-1*H*-1,2,3-triazol-1-yl)acetate* **3a**. ^{1}H NMR ($CDCl_3$) δ: 1.30 (t, 3H, *Me*CH_2, *J* 7.1 Hz), 4.27 (q, 2H, Me*C*H_2, *J* 7.1 Hz), 5.47 (s, 2H, CH_2). ^{19}F NMR ($CDCl_3$) δ: –73.8. MS (ESI), *m*/*z*: 328.0907 $[M+H]^+$ (calc. for $C_{14}H_{13}F_3N_3O_3$, *m*/*z*: 328.0904).

*Ethyl [5-(4-*tert*-butylphenyl)-4-trifluoroacetyl-1*H*-1,2,3-triazol-1-yl]-acetate* **2g**. Colourless oil, yield 158 mg (41%). IR (ν/cm^{-1}): 1723 ($COCF_3$), 1754 (CO_2Et). ^{1}H NMR ($CDCl_3$) δ: 1.21 (t, 3H, CH_2*Me*, *J* 7.1 Hz), 1.34 (s, 9H, Bu^t), 4.19 (q, 2H, Me*C*H_2, *J* 7.1 Hz), 5.05 (s, 2H, CH_2) 7.31 (d, 2H, Ar, *J* 8.3 Hz), 7.52 (d, 2H, Ar, *J* 8.3 Hz). ^{13}C NMR ($CDCl_3$) δ: 13.8, 31.0, 34.9, 49.1, 62.6, 116.1 (q, CF_3, *J* 290.8 Hz), 120.7, 126.0, 129.0, 137.6, 145.0, 154.6, 165.6, 174.0 (q, *C*OCF_3, *J* 37.2 Hz). ^{19}F NMR ($CDCl_3$) δ: –75.2. MS (ESI), *m*/*z*: 384.1523 (calc. for $C_{18}H_{21}F_3N_3O_3$, *m*/*z*: $[M+H]^+$ 384.1530).

General remarks, procedure for the synthesis of 1,2,3-triazoles **2** and **3** using azides prepared *in situ* and characterization data of all synthesized compounds are given in Online Supplementary Materials.

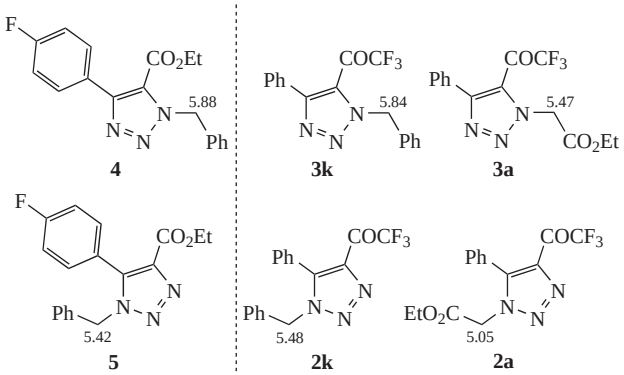


Figure 1 Chemical shifts (δ/ppm) of substituent CH_2 groups in ^{1}H NMR spectra of isomeric triazoles.

The ratio between regioisomers was determined using signals of CF_3 groups in ^{19}F NMR spectra. Alternatively, this ratio can be calculated using signals of CH_2 groups adjacent to triazole ring in ^{1}H NMR spectra. Initial structure elucidation of the isomers was performed by analyzing values of chemical shifts of these groups. According to reported data for analogous isomeric triazoles **4** and **5** containing electron-withdrawing CO_2Et group, the CH_2 signal of 1,5-isomers is downfield shifted by ~0.46 ppm as compared to 1,4-isomer[10] (Figure 1). Taking into account these data we elucidated structures of **3k** and **3a** exhibiting signals of CH_2 group in low field (5.84 and 5.47 ppm, respectively) as 1,5-isomers, whereas **2k** and **2a** (5.48 and 5.05 ppm, respectively) have a structure of 1,4-isomers.

For ultimate assignment of the isomers, investigation of triazole **2g** by ^{1}H, ^{13}C NMR and 2D experiments COSY, HSQC, HMBC and NOESY (solution in $CDCl_3$, 303 K, Bruker AV-600, for parameters of experiments see ref. 11) was performed. First, ^{1}H NMR spectrum reveals a triplet and a quartet of the ester ethyl group, two multiplets of the *para*-disubstituted benzene group (AA′XX′ spin system), and two singlets in aliphatic region with integral intensities of 2 and 9 corresponding to methylene and *tert*-butyl groups. Crucial information for regioisomeric assignment follows from the cross-peaks of *ipso*- and C^4 carbons with protons of the methylene group in the HMBC spectrum (Figure 2). The final structural confirmation was obtained from the NOESY experiment which provided the large value (3.1%) of the observed NOE factor (*cf.* ref. 11).

The classical method for the synthesis of azides is the nucleophilic substitution of halogen in the corresponding alkyl halides using sodium azide, regularly in DMSO or DMF. We suggested that, starting from alkyl bromides, it could be possible to synthesize the corresponding azides *in situ* and use them in the reaction with CF_3-ynones. To examine this assumption, one-pot reaction with a number of aliphatic bromides, two benzylic bromides, and ethyl bromoacetate was studied. The reaction was carried out in two steps. Firstly, bromide **6** and sodium azide were mixed in DMSO and left for 24 h at room temperature. After this, CF_3-ynone was added and the mixture was heated at 80–90 °C for 7 h. In this manner, the target triazoles were obtained, although

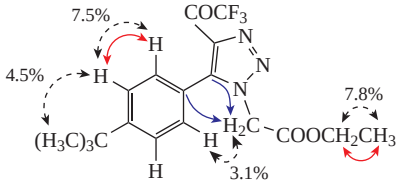
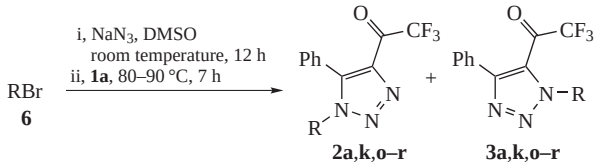


Figure 2 Structure of compound **2g**. The arrows schematically show the main correlations due to interproton couplings $^nJ_{HH}$ (double-edged solid arrows), long-range couplings $^nJ_{CH}$ (solid arrows), and NOE factors (double-edged dashed arrows).



	R	Yield of **2** + **3** (%)	**2** : **3** ratio
a	CH_2CO_2Et	62	94 : 6
k	Bn	58	96 : 4
o	$Ph(CH_2)_2$	30	99 : 1
p	$Ph(CH_2)_3$	42	98 : 2
q	$4\text{-}O_2NC_6H_4CH_2$	34	100 : 0
r	$n\text{-}C_5H_{11}$	31	97 : 3

Scheme 3 Synthesis of trifluoroacetyltriazoles by the reaction of azides obtained *in situ*.

in slightly lower yields (Scheme 3). Decrease in the yields can be attributed to the side reactions, for example, reaction of residual azide anion with ynone **1**. However, the proposed approach avoids the stage of isolation of potentially explosive azides, which is an advantage of the method.

In conclusion, the reaction between CF_3-ynones and azides proceeds with good regioselectivity in polar solvents, leading to corresponding trifluoroacetyltriazoles with content of a major regioisomer up to 95–100%. The reaction is general and allows one to involve the substrates containing various alkyl and aryl substituents in both CF_3-ynone and azide. In one-pot procedure, azides can be synthesized *in situ* from alkyl bromides and sodium azide, which enhances the preparative value of the reaction.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2018.01.003.

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