A Direct and General Synthesis of 5-Substituted 3-Trifluoromethyl-1,2,4-triazoles *via* the Three Component Condensation Reaction of Ethyl Trifluoroacetate, Hydrazine and Amidines

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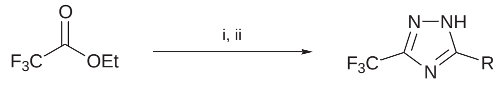
Kazumasa Funabiki,* Naoko Noma, Gouhaku Kuzuya, Masaki Matsui and Katsuyoshi Shibata*
Department of Chemistry, Faculty of Engineering, Gifu University, Yanagido, Gifu 501-1193, Japan

The three component condensation reaction of ethyl trifluoroacetate, hydrazine and amidines in the presence of sodium hydroxide in tetrahydrofuran at reflux temperature gave the corresponding 3-trifluoromethyl-5-substituted 1,2,4-triazoles in good to excellent yields.

Trifluoromethylated nitrogen-containing heterocycles have been of great interest in the medicinal and agricultural fields as well as in fluorine chemistry, because of their unique and potent biological and physiological activities. Although a number of methods for the synthesis of these compounds have been reported,[1] there are only few successful examples for ring-trifluoromethylated 1,2,4-triazole derivatives, irrespective of their versatile utilities as a herbicide, and/or insecticide.[2] Existing methodologies, however, require multistep manipulation, expensive starting materials and low applicability of the reaction resulting in relatively low yields. Therefore, it is of great significance to develop a more convenient and direct access to such compounds.

In our continuing studies on the highly efficient and regiocontrolled synthesis of trifluoromethylated nitrogen-containing heterocycles,[3] we describe herein the direct and general access to 5-substituted 3-trifluoromethyl-1,2,4-triazoles, which consists of the three-component condensation reaction of ethyl trifluoroacetate, hydrazine and amidines.[4]

Successive treatment of ester **1** with a 0.8 equimolar amount of hydrazine in tetrahydrofuran (THF) at reflux temperature for 1 h and with a 1.1 equimolar amount each of benzamidine hydrochloride and sodium hydroxide (NaOH) for 3 h produced 3-trifluoromethyl-5-phenyl-1,2,4-triazole **2a** in 80% yield (Scheme 1, Table 1, entry 2).



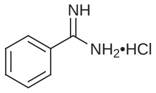
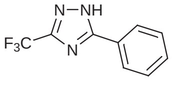
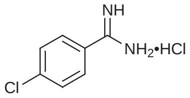
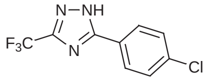
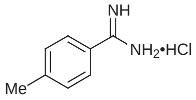
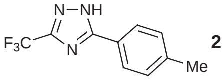
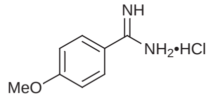
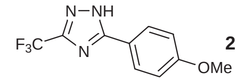
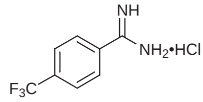
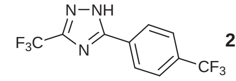
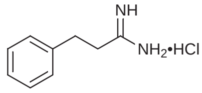
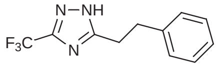
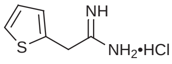
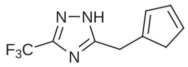
1 **2**

Scheme 1 *Reagents and conditions*: i, 0.8 equiv. $NH_2NH_2\cdot H_2O$, THF, reflux, 1 h, ii, 1.1 equiv., $RC(=NH)NH_2\cdot HCl$, 1.1 equiv., NaOH, THf, reflux, 3 h.

The reaction at room temperature resulted in the lower yield of **2a** than that at reflux (entry 1). Acetonitrile or ethanol as the solvent provided **2a** in 78 and 57% yields, respectively (entries 3 and 4). The use of potassium *tert*-butoxide (Bu^tOK) as the base led to the formation of **2a** in 60% yield (entry 5). Triethylamine was insufficient for the reaction, producing only a 10% yield of the product, presumably due to its lower basicity than the amidine (entry 6).[5]

The results of the three-component condensation reaction are summarized in Table 1. Other amidine hydrochloride successfully participated in the reaction to give the corresponding 5-substituted 3-trifluoromethyl-1,2,4-triazole derivatives **2** in good to excellent yields (entries 7–12).

Table 1 Synthesis of 5-substituted 3-trifluoromethyl-1,2,4-triazoles **2**[a]

Entry	Amidine hydrochloride	Triazole		Yield[b] (%) of **2**
1[c]			**2a**	49
2			**2a**	80
3[d]			**2a**	78
4[e]			**2a**	57
5[f]			**2a**	60
6[g]			**2a**	10
7			**2b**	62
8			**2c**	74
9			**2d**	70
10			**2e**	63
11			**2f**	73
12			**2g**	94

[a] Unless otherwise noted, all reactions were carried out with ethyl trifluoroacetate (1 mmol), hydrazine monohydrate (0.8 mmol), amidine hydrochloride (1.1 mmol) and NaOH (1.1 mmol) in THF (5 mL) at reflux. [b] Isolated yields. [c] Conducted at room temperature. [d] Acetonitrile used as solvent. [e] Ethanol used as solvent. [f] Bu^tOK used as base. [g] Et_3N used as base.

Scheme 2 shows a plausible mechanism for the formation of **2**.

Trifluoroacetic acid hydrazide **3** is initially formed by the reaction of the ester **1** with hydrazine monohydrate. This then reacts with amidine, which had been generated from amidine hydrochloride and NaOH, producing trifluoroacetyl amidrazone **4**, followed by tandem cyclization-dehydration to give the 5-substituted 3-trifluoromethyl-1,2,4-triazole **2**.

In summary, we succeeded in the efficient synthesis of 5-substituted 3-trifluoromethyl-1,2,4-triazoles by the one-pot condensation reaction of ethyl trifluoroacetate, hydrazine

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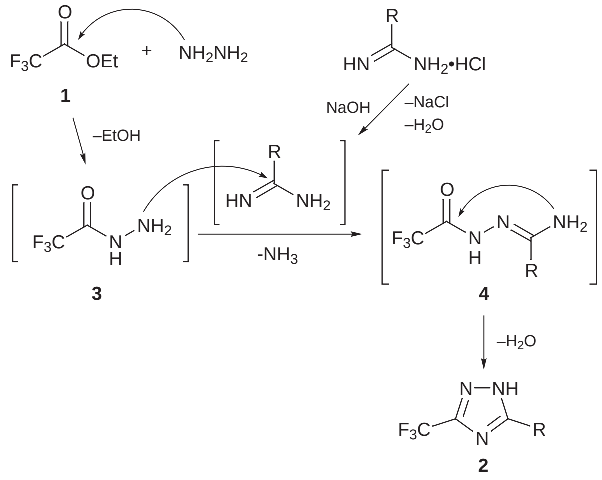
* To receive any correspondence (*e-mail*: kfunabik@apchem.gifu-u.ac.jp).



Scheme 2

and amidines. This method can serve as a general, practical and direct route to 5-substituted 3-trifluoromethyl-1,2,4-triazoles, which will be an important frame as a herbicide and/or insecticide.

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Techniques used: ^{1}H and ^{19}F NMR, MS

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