A Convenient One-Pot Synthesis of 7-Trifluoromethyl-Substituted Imidazo[4,5-*b*]pyridines

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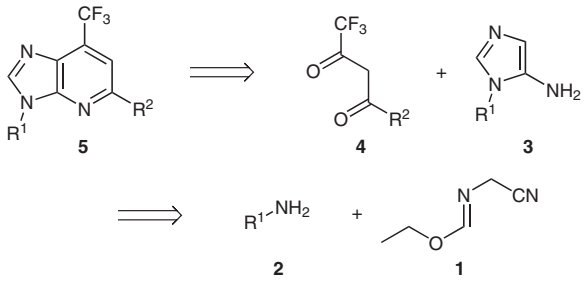
Abstract: This communication describes a practical and facile one-pot approach for the synthesis of 7-trifluoromethyl-substituted imidazo[4,5-*b*]pyridines by the reaction of in situ generated 5-aminoimidazole and a 1,3-CCC-biselectrophile.

Key words: cyclizations, fluorine, heterocycles, imidazopyridines, aminoimidazoles

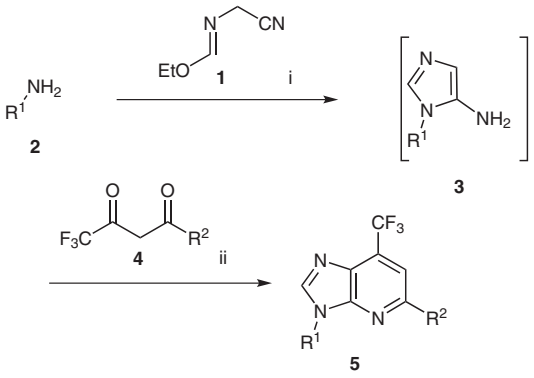
Imidazo[4,5-*b*]pyridines are an important class of biologically active compounds showing anticancer,[1] antiviral,[2] antimitotic,[3] and tuberculostatic[4] properties depending on the nature and position of substituents within the heterocycle. These compounds are typically prepared by condensation of an appropriate *o*-diaminopyridine and an electrophilic carbon unit.[5]

To avoid the synthesis of highly substituted *o*-diaminopyridines, which are not easy accessible, we developed an alternative access to imidazo[4,5-*b*]pyridine starting from ethyl *N*-(cyanomethyl)-formimidate (**1**) by a two-step cyclocondensation with any amine of type **2a**–**i** to obtain in a one-pot procedure the corresponding 5-aminoimidazole **3**. There was no need for reduction[6] or decarboxylation.[7] Hence, after the in situ synthesis of 5-aminoimidazole another cyclocondensation with a trifluormethyl-containing building block **4a**–**e** follows to obtain selectively the 7-trifluoromethyl-substituted imidazo[4,5-*b*]pyridines **5**. The convergent manner of this approach allows the synthesis of versatile substituted imidazo[4,5-*b*]pyridines depending on amine and 1,3-electrophilic reagents (Scheme 1).

Since it is known that the insertion of perfluoroalkyl substituents in bioactive molecules leads to an increase of lipid solubility, and thereby enhances the adsorption rate and the transportation in vivo,[8] heterocyclic compounds bearing a trifluoromethyl group are the subject of continuous interest due to their potent pharmacological properties. Basically, there are two important ways to insert a trifluoromethyl group in a heterocylic system. One is the organometallic mediated exchange form bromine or iodine substituent with a trifluoromethyl group.[9] However, the most widespread method to produce heterocycles with a trifluoromethyl group is assembly from trifluoromethyl-containing building blocks. Recently, the most popular trifluoromethyl-containing building blocks have been the



Scheme 1 Retrosynthetic approach



Scheme 2 *Reagents and conditions*: (i) amine, CH_2Cl_2, reflux, formimidate **1**, reflux, 3 h; (ii) 1,3-diketone (1 equiv), reflux, 8 h.

following 1,3-electrophilic reagents: 4-trifluoromethyl-1,3-diones,[10] alkoxyvinyl trifluoromethyl ketones,[11] β-trifluoroacetylvinylsulfones,[12] and trifluoroacetimidoyl halides.[13]

To evaluate the feasibility of our concept, we first optimized the cyclization conditions. The starting material ethyl *N*-(cyanomethyl)formimidate, which was accessible in three steps beginning from formaldehyde and KCN,[14–16] is highly sensitive to moisture. The cyclization was carried out under an inert-gas atmosphere using dried reagents. Use of the solvents such as ethanol, acetonitrile, and DMF resulted in poor yields and many byproducts. The solvent resulting in the best yields and only little byproduct was dichloromethane (Scheme 2). Hence, all following reactions were carried out in dried CH_2Cl_2.[17]

The method was applicable for a number of amines (Table 1).

Now, the method should be extended to other 1,3-biselectrophiles such as **4a**–**e** to obtain a variation in the decoration of the imidazo[4,5-*b*]pyridine scaffold. We used the

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Table 1 Variation of N3 Substitution Depending on Initial Amine **2**

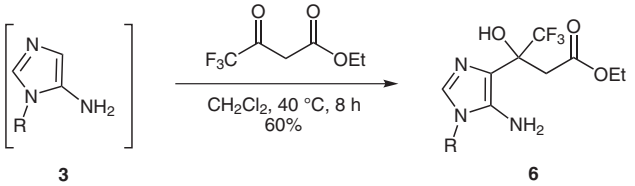
Compound	Amine	Product	Yield (%)[a]
5a	Benzylamine	R^1 = Bn R^2 = Ph	70
5b	Benzylamine	R^1 = Bn R^2 = Me	88
5c	(4-Metoxyphenyl)methyl amine	R^1 = PMB R^2 = Me	55
5d	(2,4-Dimethoxyphenyl)methyl amine	R^1 = 4,2-Dimetoxybenzyl R^2 = Me	68
5e	1,1-Diphenylmethyl amine	R^1 = 1,1-Diphenylmethyl R^2 = Me	41
5f	(*R*)-1-Phenylethyl amine	R^1 = (*R*)-1-(1-Phenylethyl) R^2 = Me	56
5g	2,2-Dimethoxyethyl amine	R^1 = 2,2-Dimethoxyethyl R^2 = Me	50
5h	(*R*)-1-Cyclohexylethyl amine	R^1 = (*R*)-1-(1-Cyclohexylethyl) R^2 = Me	85
5i	(*S*)-1-Cyclohexylethyl amine	R^1 = (*S*)-1-(1-Cyclohexylethyl) R^2 = Me	89
5j	2-(4-Methoxyphenyl)ethyl amine	R^1 = 2-(4-Methoxyphenyl)ethyl R^2 = Me	50

[a] Yields refer to isolated products.

same reaction procedure described above, varying the biselectrophile. The yields decreased with the number of fluorine substituents in the 1,3-biselectrophiles (Table 2).

During the reaction with 4,4,4-trifluoro-3-oxybutyrate it was possible to isolate the intermediate **6** (Scheme 3). This result is consistent with the work by Volochnyuk et al.[18] The chemical shift of the neighbor carbon of CF_3 is δ = 74 ppm [^{13}C NMR (100 MHz, $CDCl_3$)] and δ = –82 ppm [^{19}F NMR (376 MHz, $CDCl_3$)], indicating that the condensation was not complete. This kind of intermediate can only be isolated with the 3-oxybutyrate derivative. With the 1,3-diketones, these intermediates were not observed, because of the higher reactivity.

During the experiments a considerable regioselectivity could be observed. With asymmetric trifluoromethyl-containing 1,3-diketones only the γ-CF_3 substituted imidazopyridines were isolated. The structure determination was carried out by ^{13}C NMR, ^{1}H NMR, and X-ray crystallography. In the case of the ^{13}C NMR analyses, the spin–spin coupling of fluorine and carbon was a useful tool. The neighbor carbon atom to the CF_3 group is split up to a quartet with a spin–spin coupling constant of about $^2J_{CF}$ = 34 Hz. The observed chemical shift of the carbon atom situated *para* to the pyridine nitrogen is about δ = 130 ppm (100 MHz, $CDCl_3$). The C2 carbon atom in the pyridine has a chemical shift of about δ = 150 ppm (100 MHz, $CDCl_3$). In our experiments we could only isolate trifluoromethyl-substituted compounds where the C4 carbon atom shows a chemical shift about δ =130 ppm and a quartet with the coupling constant about *J* = 30 Hz. This is a clear evidence for the desired regiochemistry. In addition, we confirmed the substitution pattern by a X-ray structure analysis of compound **5a**.[19]



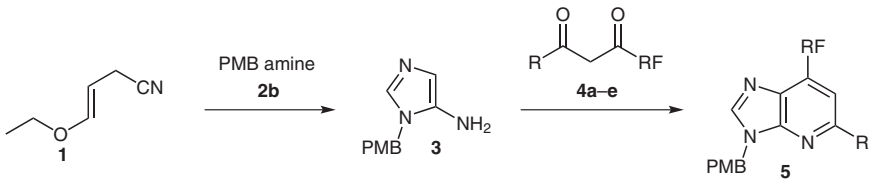
3 6

Scheme 3 In situ generated 5-aminoimidazoles react with ethyl 4,4,4-trifluoro-3-oxibutyrate without ring closing to intermediate **6**

The regioselectivity could be explained with the known characteristics of of 5-aminoimidazole and asymmetric trifluoromethyl-containing 1,3-diketones. The aminoimidazoles are N,C-ambident nucleophiles. Ramsden et al.[20] studied the chemical behavior of aminoimidazoles. According to them, the side of reaction was confirmed by AM1 calculations on the aminoimidazole structure and by synthetical experiments. Thus, the C4 carbon atom favors addition of soft electrophiles (low-energy LUMO) at this position, whereas the exocyclic amino function prefers the addition of hard electrophiles.

The trifluoromethyl ketones are known as highly reactive electrophilic carbonyl compounds. Studies by Linderman and Jamois[21] show that the acceptor orbital (LUMO) energy level for fluoroketones are about 21.2–28.4 kcal/mol

Table 2 Variation of Scaffold Substitution Pattern Depending on Initial 1,3-Biselectrophile



Compound	R	R_F	Yield (%)[a]
5k	Me	CF_3	55
5l	Ph	CF_3	60
5m	Me	C_2F_5	23
5n	Me	CHF_2	48
5o	CF_3	CF_3	25

[a] Yields refer to isolated products.

lower than the LUMO energy level of the nonfluorinated analogues. These properties and our experimental results in mind we suppose, that the regiochemistry could be explained by the hard–soft acid–base (HSAB) principle.[22] We could not yet observe other effects which control the regioselectivity.

In summary, we have developed a useful tool to synthesize 5,7-disubstituted imidazo[4,5-*b*]pyridines in a one-pot reaction. With this approach it was possible to introduce a CF_3 group selectively in *para* position to the pyridine nitrogen.

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(17) **General Procedure**
A solution of amine **2a–i** (5 mmol) in dried CH_2Cl_2 (2,5 mL) was heated until reflux. After a period of 15 min ethyl *N*-(cyanomethyl)formimidate **1** (5 mmol, 560 mg) was added under N_2 counterflow. The mixture was allowed to stir

under reflux for 2 h. To the hot reaction mixture the 1,3-biselectrophile of type **4a–e** (5 mmol) was added. The mixture was stirred for 8 h. Then it was cooled down to ambient temperature. The crude product was worked up through flash column chromatography to obtain the product as white needles.

Selected Data for 5o

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.79 (s, 3 H, OCH_3), 5.47 (s, 2 H, CH_2), 6.89 (m, 2 H, Ph), 7.33 (m, 2 H, Ph), 7.87 (s, 1 H, H-6), 8.31 (s, 1 H, H-2). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 47.5 (OCH_3), 55.3 (CH_2), 111.5 (m, C-6), 122.3 (q, $^1J_{CF}$ = 278 Hz, CF_3), 121.6 (q, $^1J_{CF}$ = 278 Hz, CF_3), 114.4 (Ph), 126.6 (Ph), 130.1 (Ph), 160.4 (Ph), 129.7 (q, $^2J_{CF}$ = 36 Hz, C-7), 133.6 (C-7a), 143.1 (q, $^2J_{CF}$ = 35 Hz, C-5), 148.4 (C-3a), 148.6 (C-2). ^{19}F NMR (376 MHz, $CDCl_3$): δ = –62.59, –66.55.

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