SYNTHESIS A NEW 4-SULFONYL-5-FORMYL-1*H*-IMIDAZOLES

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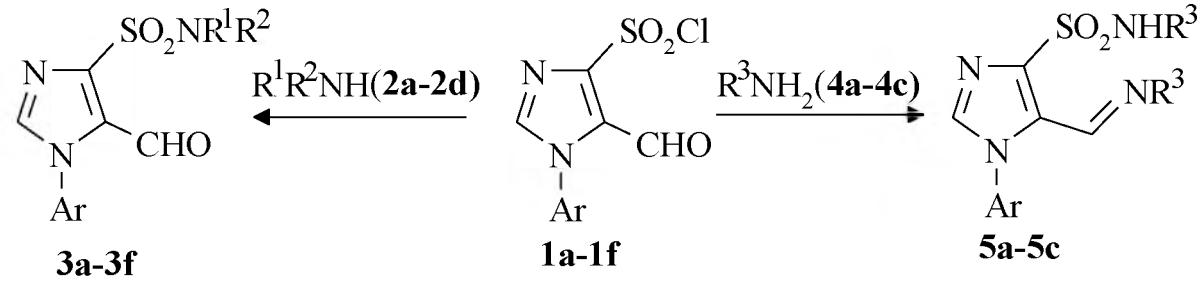
4-Sulfonylimidazole fragment is a potent pharmacophore which is widely used in the design of biologically active compounds. Most frequently, this fragment is introduced into target structures with the aid of 1-methylimidazole-4-sulfonyl chloride. The starting compounds were 1-aryl-5-formyl-1H-imidazole-4-sulfonyl chlorides **1a–1f** obtained by us previously [1].

It seemed reasonable to study reactions of **1a–1f** with nitrogen and oxygen nucleophiles with the goal of estimating their synthetic potential and the effect of the imidazole ring therein on the reactivity of functional groups. Sulfonyl chlorides **1a–1f** reacted with acyclic and cyclic secondary amines **2a–2d** in boiling acetonitrile in the presence of triethylamine to produce 1-aryl- 5-formyl-1*H*-imidazole-4-sulfonamides **3a–3f** in 85–90% yield as a result of replacement of the chlorine atom by amino group. The reactions of compounds **1** with primary alkyl- and arylamines **4a–4c** were always accompanied by condensation at the aldehyde group. When the reactant ratio was 1 : 1, complex mixtures of products were formed, which contained (according to the GC/MS data) the corresponding Schiff bases, disubstituted derivatives, and a number of unidentified compounds. However, by reacting sulfonyl chlorides **1e** and **1f** with 2 equiv of amines **4a–4c** under the conditions described for secondary amines, we succeeded in isolating N-substituted 1-aryl-5-imino- 1*H*-imidazole-4-sulfonamides **5a–5c** in 72–79% yield (Scheme1).

Scheme 1



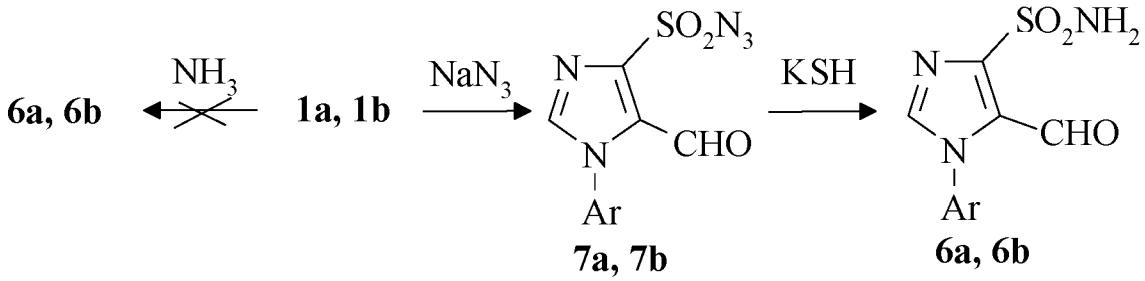
3a-3f **1a-1f** **5a-5c**

1, Ar = Ph (**a**), 2-BrC6H4 (**b**), 3-MeC6H4 (**c**), 4-ClC6H4 (**d**), 4-MeC6H4 (**e**), 4-MeOC6H4 (**f**). **2**, $R^1 = R^2$ = Et (**a**); R^1R^2 = (CH2)4 (**b**), (CH2)5 (**c**), (CH2)2O(CH2)2 (**d**); **3**, Ar = Ph, $R^1 = R^2$ = Et (**a**); R^1R^2 = (CH2)5 (**b**), (CH2)2O(CH2)2 (**c**); Ar = 2-BrC6H4, R^1R^2 = (CH2)4 (**d**); Ar = 4-ClC6H4, R^1R^2 = (CH2)5 (**e**); Ar = 4-MeC6H4, R^1R^2 = (CH2)4 (**f**); **4**, R^3 = Me (**a**), PhCH2 (**b**), 4-MeC6H4 (**c**); **5**, Ar = 4-MeC6H4, R^3 = Me (**a**); Ar = Ph, R^3 = PhCH2 (**b**); Ar = R^3 = 4-MeC6H4 (**c**).

In the reaction of sulfonyl chloride **1a** with ammonia we obtained a mixture of products containing no more than 22% of 5-formylimidazole-4-sulfonamide **6a**. Presumably, the reaction of **1** with ammonia follows a more complicated scheme, and simple preparative synthesis of N-unsubstituted 5-formylimidazole-4-sulfonamides **6** in this way is hardly possible.

In order to obtain sulfonamides **6a** and **6b**, sulfonylchlorides 1a and 1e were preliminarily converted to 1-aryl-5-formyl-1H-imidazole-4-sulfonyl azides **7a** and **7b** by treatment with excess sodium azide in DMF at room temperature. Mild reduction of **7a** and **7b** with potassium hydrogen sulfide in ethanol at 0–5°C selectively afforded 1-aryl-5-formyl-1H-imidazole-4-sulfonamides **6a** and **6b** in 69–75% yield (Scheme 2).

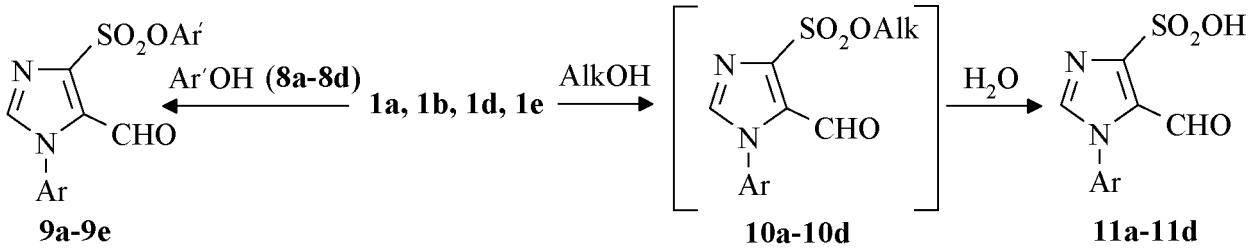
Scheme 2



Ar = Ph (**a**), 4-MeC6H4 (**b**).

It was expected that reactions of sulfonyl chlorides 1 with phenols and alcohols would provide a convenient synthesis of alkyl and aryl imidazolesulfonates. In fact, sulfonyl chlorides 1a, 1b, 1d, and 1e smoothly reacted with phenols 8a–8d in boiling acetonitrile (1 h) in the presence of triethylamine to give aryl sulfonates 9a–9e in 75–82% yields. However, we failed to obtain alkyl analogs 10a–10d under analogous conditions, i.e., by heating compounds 1a, 1b, 1d, and 1e with an equimolar amount of methanol or ethanol. On the other hand, by refluxing the same substrates in excess alcohol for 1 h we obtained 1-aryl-5-formyl-1H-imidazole-4-sulfonic acids 11a–11d with high yields (Scheme 3). Obviously, alkyl sulfonates 10 are unstable, and they readily undergo hydrolysis to the corresponding sulfonic acids.

Scheme 3



8, Ar′ = Ph (**a**), 4-MeC6H4 (**b**), 4-(OCH)C6H4 (**c**), 2-OCH-5-MeOC6H3 (**d**); **9**, Ar = Ph, Ar′ = 4-MeC6H4 (**a**); Ar = 4-MeC6H4, Ar′ = Ph (**b**); Ar = 2-BrC6H4, Ar′ = 4-(OCH)C6H4 (**c**); Ar = 4-ClC6H4, Ar′ = 4-(OCH)C6H4 (**d**); Ar = 4-MeC6H4, Ar′ = 2-OCH-5-MeOC6H3 (**e**); **10**, **11**, Ar = Ph (**a**), 2-BrC6H4 (**b**), 4-ClC6H4 (**c**), 4-MeC6H4 (**d**).

This reaction may be regarded as an efficient method of synthesis of acids 11, since the yield of the latter in the direct hydrolysis of sulfonyl chlorides 1 in aqueous tetrahydrofuran did not exceed 40%

1. Dorokhov V. I, Grozav A. N., Chornous V. A., Vovk M. Synthesis a new 5-formylimidazole-4-sulfonyl chlorides // Збірник наукових праць V Всеукраїнської наукової конференції «Актуальні задачі хімії: дослідження та перспективи». – Житомир : ЖДУ ім. І. Франка, 2021, С 230-231.