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Synthesis of functionalized *m*-bistrifluoromethylbenzenes via cyclocondensation of 1,1,1,5,5,5-hexafluoroacetylacetone with enamines

Dmitriy M. Volochnyuk, Alexander N. Kostyuk,* Dmitriy A. Sibgatulin and Alexander N. Chernega

Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Murmanskaya 5, 02094 Kyiv-94, Ukraine

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Abstract—The reaction of 1,1,1,5,5,5-hexafluoroacetylacetone with push–pull enamines having a methyl group at the α-position was investigated. It was found that the reaction is sensitive both to the structure of enamines and to reaction conditions. As a result, a set of bistrifluoromethyldialkylanilines and ethyl bistrifluoromethylsalicylate was prepared. Plausible mechanisms and factors influencing the course of the reaction are discussed.

1. Introduction

Introduction of the trifluoromethyl group, an important functional group in organic chemistry allows chemists to considerably change physico-chemical properties of organic molecules.[1] Thus, derivatives of *m*-bistrifluoromethylbenzene are actively used in the design and synthesis of various ligands[2] and pharmaceutical substances.[3,4] Further development of methods for synthesis of functionalized *m*-bistrifluoromethylbenzenes is investigated. Although this fragment is actively used in many pharmaceutical research projects, in almost all of them 3,5-trifluoromethylaniline is used due to a known synthetic procedure described years ago.[5]

A few works such as the palladium catalyzed arylation of amines with 1-bromo-3,5-bis(trifluoromethyl)benzene[6] and the use of 2-methoxy-4,6-bis(trifluoromethyl) phenyllithium[7] give alternative approaches to the synthesis of bistrifluoromethylbenzene derivatives.

At the same time the commercially available symmetrical 1,3-biselectrophilic building block—1,1,1,5,5,5-hexafluoroacetylacetone has been used for synthesis of bistrifluoromethylated heterocyclic compounds. This approach has proved to be one of the most convenient methods for the synthesis of bistrifluoromethylated pyrazoles, isoxazoles,[8] pyridines,[9] pyrimidines,[10] pyrroles,[11] and diazepines.[12] To the best of our knowledge, the approach has not been applied to the synthesis of bistrifluoromethylated benzenes yet. In our previous work we have demonstrated the possibility of using tertiary push–pull enamines as 1,3-*CCC*-bisnucleophiles in the reactions with β-trifluoroacetylvinyl ethers for synthesis of monotrifluoromethylated functionalized dialkylanilines.[13] In this work we report our results on the reaction of tertiary push–pull enamines having a methyl group at the α-position with 1,1,1,5,5,5-hexafluoroacetylacetone **1**.

2. Results and discussion

2.1. Interaction of 1,1,1,5,5,5-hexafluoroacetylacetone with β-dialkylaminocrotonitriles

Enamines **2** derivatives of β-aminocrotonitrile react with 1,1,1,5,5,5-hexafluoroacetylacetone **1** in benzene at room temperature for 2–3 days affording a mixture of arene hydrate **3** and diol **4** in combined yield 35–40%, precipitated from the reaction mixture. Analysis of the reaction mixture by ^{19}F NMR reveals presence of the starting β-diketone **1** and traces of benzenes **5**. Numerous attempts to optimize the reaction conditions failed. Increasing the reaction temperature or time lead to formation of benzenes **5** and pyridone **6** products of the self-condensation of enamines **2**. Carrying

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* Corresponding author. Tel.: +380 44 5373218; fax: +380 44 5373253; e-mail: a.kostyuk@enamine.net

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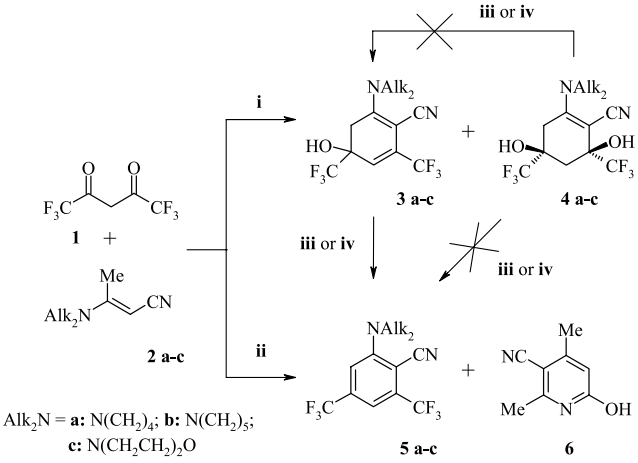
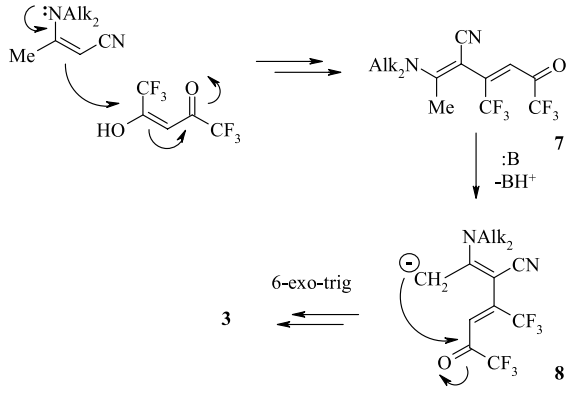
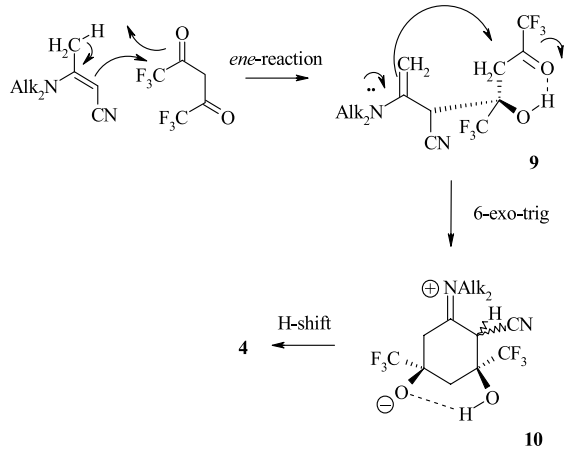


Scheme 1. Reagents and conditions: (i) benzene, rt, 2–3 days; (ii) benzene, reflux, 2 h; (iii) acetone, rt, 7–10 days; (iv) toluene, PTSA, reflux, 30 min.

out the reaction in boiling benzene or methanol results in conversion of 60–70% of the starting enamine, but the ratio of cyclization product **4** to pyridone **6** is ca. ~7:1 for enamine **2a**, and ~4:6 for enamine **2c** (Scheme 1). The ratio of reaction products **3** and **4** depends on the structure of the dialkylamino residue and reaction conditions (Table 1). Thus, for pyrrolidine enamine **2a**, the diol was registered in trace amount, while in the case of morpholine enamine **2c**, the ratio of diol/'hydrate' was 1:1. At the same time for enamine **2c**, diol **4c** was not registered at all when the reaction was run at 40–50 °C. It is worth noting that under the conditions in which hydrates **3** are transformed into benzenes **5**, diol **4** remains intact. Thus, we can draw the conclusion that diols **4** are not intermediate products in the chain of transformations **2**→**3**→**5**. We suppose that formation of **3** and **4** proceeds by different mechanisms. In the case of **3**, hexafluoroacetylacetone **1** reacts as an enol affording dienamine **7**, followed by 6-*exo-trig* cyclization to give 'hydrate' **3** (Scheme 2). At the same time the key step in the formation of diol **4** is the *ene*-reaction of enamines **2** with hexafluoroacetylacetone **1** which react in the ketone form like MeTFP,[14] affording terminal enamines **9** followed by spontaneous cyclization into diol **4**. Formation of only one possible diastereomer of **4** whose stereochemistry was solved by the single X-ray diffraction study could be rationalized by intramolecular hydrogen bonding (Scheme 3). Indirect proof for the proposed mechanisms is the growth of the 'hydrate' **3** produced upon increase of *C*-nucleophilicity of the enamines. Higher nucleophilicity would facilitate the reaction presented on Scheme 2,[13] and would not influence the reaction given on Scheme 3.[14]



Scheme 2.



Scheme 3.

The structures of compounds synthesized were confirmed by a set of physico-chemical methods, and for compounds **3a** and **4c** single X-ray diffraction studies were accomplished. (Figs. 1 and 2). It is worth noting that compounds of type **3** are allied to so-called arene hydrates whose simple representatives are highly unstable compounds under normal conditions.[15] In our previous work[13] two types of arene hydrates (type **A** and **B**, Fig. 3) which are stable under normal conditions have been described. In our viewpoint their stability is stipulated both by kinetic and thermodynamic factors. Substances **3** like arene hydrates of type **A** and **B** are stable compounds in the solid state, melting without decomposition. On heating in solution in the presence of catalytic amounts of acids such as PTSA 'arene hydrates' **3** eliminate water irreversibly turning into the corresponding benzenes **4**. It should be noted that arene

Table 1. Yields of products of the reaction of enamines **2** with hexafluoroacetylacetone **1**

Enamine	Conditions	Yield (%)			
		3	**4**	**5**	**6**
2a[a]	C_6H_6, rt, 3 days	31	Traces	6	—
2b[a]	C_6H_6, rt, 3 days	26	9	3	—
2c[a]	C_6H_6, rt, 3 days	21	23	5	—
2c[a]	C_6H_6, 40 °C, 3 h	14	Traces	15	—
2a[b]	C_6H_6, reflux, 4 h	—	—	43	6
2c[b]	C_6H_6, reflux, 4 h	—	—	28	24

[a] Refer according to ^{19}F NMR spectra of reaction mixture.
[b] Yields of **5** refer according to ^{19}F NMR spectra of reaction mixture and yield of **6** is for isolated product.