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# An efficient access to (1*H*-tetrazol-5-yl)furoxan ammonium salts via a two-step dehydration/[3+2]-cycloaddition strategy

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ABSTRACT

A general, highly effective two-step approach for direct synthesis of (1*H*-tetrazol-5-yl)furoxan ammonium salts with various functional substituents based on initial effective synthesis of cyanofuroxans by dehydration of furoxancarboxylic acid amides by the action of $(CF_3CO)_2O$/Py followed by [3+2]-cycloaddition of cyanofuroxans to ammonium azide, generated in situ from $TMSN_3$ and $NH_4F$, has been developed.



## 1. Introduction

An effective approach to the creation of new drug candidates with improved pharmacokinetic profiles is the design of new structures by molecular hybridization of different compounds, first of all, heterocyclic derivatives, with known pharmacological activity.[1] In recent years, the 1,2,5-oxadiazole 2-oxide (furoxan) moiety has been the subject of increased attention, pioneered by Gasco and others, owing to an abundance of interesting biological activities related to the ability of furoxans to release nitrogen oxide (NO).[2] Later, a family of hybrid structures representing a combination of various pharmacologically active compounds with furoxan ring, potential NO donor, in one molecule was synthesized.[3–6] Furthermore, furoxan derivatives may be useful as precursors for the synthesis of other azoles[7a–c] (including the widely known Boulton–Katritzky rearrangement)[7d–f] and they are also of interest as components of high enthalpy formulations.[8] Taking into account these features of the furoxan ring, it is expedient to combine in one molecule the furoxan ring with other heterocyclic moieties, possessing both pharmacological activity and positive formation enthalpy. Considering this goal, tetrazole is an appropriate heterocycle.

The 1*H*-tetrazole functional group is a versatile moiety for organic synthesis known to be quite stable over a broad pH range. It has good tolerance to various oxidizing and reducing agents[9] and can be considered for carboxylic acid bioisosteres,[10] *cis*-amide isosteres in peptide chemistry[11] as well as in material science.[12] The tetrazole ring is an important pharmacophore in medicinal chemistry[13] and its pharmaceutical applications have been vastly explored and comprehensively documented in the literature.[14] Tetrazole-based drug candidates possess anticonvulsant,[15] antihypertensive, antiallergic, and antibiotic activities,[16] and have shown promising results in treatment of various diseases, such as cancer and AIDS.[17] Besides, tetrazoles are widely used in agriculture as herbicides and fungicides.[18] Owing to the high enthalpy of formation, some tetrazole derivatives have been explored in various propellant formulations.[19]

Several strategies have been proposed to produce tetrazoles;[20] however, most of the involved reactions proceed under rather harsh conditions or include metal reagents, which can pollute final products. Among these approaches, [3+2]-cycloaddition of the azide anion to nitriles remains the main synthetic route to 5-substituted 1*H*-tetrazoles, in particular, the reaction of nitriles with $NaN_3$[21] or with $TMSN_3$[22] in the presence of acidic catalysts, including acidic ionic liquids.[23] Recently, the first representatives of

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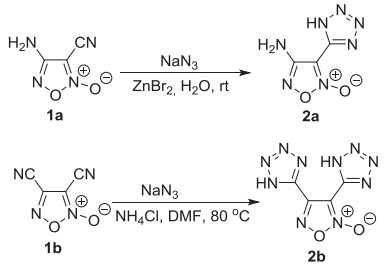
(1*H*-tetrazol-5-yl)furoxans were synthesized by these approaches.[24] The 4-amino-3-cyanofuroxan **1a** was transformed into 4-amino-3-(1*H*-tetrazol-5-yl)furoxan **2a** on treatment with $NaN_3$ in water in the presence of $ZnBr_2$,[24a] while 3,4-bis(1*H*-tetrazol-5-yl) furoxan **2b** was synthesized by the reaction of 3,4-dicyanofuroxan **1b** with $NaN_3$ in DMF at 80 °C in the presence of $NH_4Cl$ (Scheme 1).[24b,c] The preliminary conversion of the cyano groups of 3,4-dicyanofuroxan **1b** to bis(aminohydroxamoyl)furoxan followed by a three-step sequence resulted in bis(1-hydroxytetrazol-5-yl)furoxan.[24d] A number of salts of the synthesized (1*H*-tetrazol-5-yl) furoxans were prepared and investigated in these works.




**Scheme 1.** Known examples of the (1*H*-tetrazol-5-yl)furoxans.

Here we present the results of our research dealing with the development of a general method for the preparation of both 3- and 4-cyanofuroxans **1** with various functional substituents by dehydration of corresponding available furoxancarboxamides **3** by the action of $(CF_3CO)_2O$/Py and with one-pot direct access to (1*H*-tetrazol-5-yl)furoxan ammonium salts **4** or free (1*H*-tetrazol-5-yl)furoxans **2** by [3+2]-cycloaddition of the cyanofuroxans **1** to ammonium azide generated in situ from $TMSN_3$ and $NH_4F$ in MeCN at 20 °C.

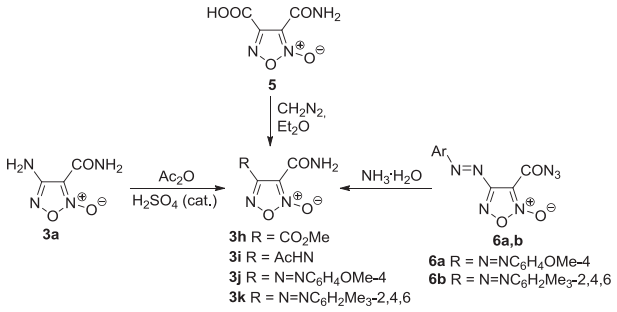
## 2. Results and discussion

### 2.1. Synthesis of cyanofuroxans

Several representatives of cyanofuroxans **1** with functional substituents are known, their synthesis being based on different synthetic approaches: oxidation of corresponding cyanoglyoxime with lead tetraacetate or $PbO_2$,[25] cyclodimerization of cyanoformonitrile oxide,[26] dehydration of furoxancarbaldehyde oxime by the action of $SOCl_2$/DMF[27] or the reaction of furoxannitrolic acid with $N_2O_4$.[28] In some works,[29] cyano group was generated by dehydration of the corresponding furoxancarboxamides by the action of $(CF_3CO)_2O$/Py/THF, but no general method for the synthesis of cyanofuroxans **1** with different functional substituents was available.

Out of the above-mentioned approaches to cyanofuroxan synthesis, we preferred the last one, because previously[30] we synthesized a series of furoxancarboxamides with different substituents. So we decided to use this approach for the preparation of both known and new cyanofuroxans **1a**–**k** with different functional substituents. The initial amides **3a**–**g** were described in the literature, amide **3h** was prepared by methylation of 3-aminocarbonyl-4-furoxancarboxylic acid **5** with diazomethane, amide **3i** was synthesized by acetylation of amide **3a**, and amides **3j**,**k** were obtained by nucleophilic substitution of azide group in 4-arylazo-3-azidocarbonylfuroxans **6a**,**b** on treatment with aqueous ammonia (Scheme 2).

It was found that $(CF_3CO)_2O$/Py is an appropriate reagent for the preparation of cyanofuroxans **1a**–**k** in high yields (70–97%) by dehydration of amides **3a**–**k** (Table 1). The reaction occurs under very mild conditions (0 °C→20 °C) over 0.5–24 h (TLC monitoring), has excellent functional group tolerance and proceeds whether the amide group is at C(3) or C(4) of the furoxan ring. For the preparation of cyanofuroxans **1a**,**b**,**f**,**i** (Table 1, entries 1, 2, 6, 9), dry MeCN was required since the reactions in dry $CH_2Cl_2$ did not result in the desired products due to insolubility of the initial compounds **3a**,**b**,**f**,**i**.




**Scheme 2.** Synthesis of the amides **3h**–**k**.

### 2.2. Synthesis of (1*H*-tetrazol-5-yl)furoxan ammonium salts 4 and free (1*H*-tetrazol-5-yl)furoxans 2

First, we performed a wide search for the optimal conditions for [3+2]-cycloaddition of cyanofuroxans **1** to the azide anion for the preparation of (1*H*-tetrazol-5-yl)furoxans **2**. The conditions used for the synthesis of 3,4-bis(1*H*-tetrazol-5-yl)furoxan **2b** ($NaN_3$ in DMF at 80 °C in the presence of $NH_4Cl$)[24b] proved to be suitable only for the synthesis of 3-methyl-4-(1*H*-tetrazol-5-yl)furoxan **3c** in moderate yield (48%), while other cyanofuroxans containing functional groups, e.g., substrates **1e**,**f**, decomposed under these conditions, apparently, due to high sensitivity of the furoxan ring to nucleophilic inorganic bases (e.g., alkalis)[31] (Table 2, entries 1, 2). And so to prepare (1*H*-tetrazol-5-yl)furoxans **2** with various substituents, dicyanoazofuroxan **1e** was chosen as the model compound for screening the reaction conditions. The reaction of compound **1e** with $NaN_3$ in water in the presence of $ZnBr_2$ used previously for the synthesis of tetrazolylfuroxan **1a**[24a] also failed (Table 2, entry 3).

Therefore, we replaced $NaN_3$ by $TMSN_3$ and screened the reaction conditions for the preparation of 3,3′-bis(1*H*-tetrazol-5-yl)-4,4′-azofuroxan **2e** by varying the ratios of solvents, catalysts, temperature, and reactants. The use of excess $TMSN_3$ in DMF or in a DMSO/MeOH mixture did not give target compound **2e** (Table 2, entries 4, 5). Therefore, TBAF and $NH_4F$ were applied as additives. The reaction of compound **1e** with excess $TMSN_3$ in the presence of TBAF in DMSO did not give the desired outcome either (Table 2, entry 6). Only replacement of DMSO by MeCN with addition of $NH_4F$ resulted in the synthesis of the target product (Table 2, entries 8–13). The catalytic amount of $NH_4F$ was ineffective (Table 2, entry 7), while increase in the amount of $NH_4F$ unexpectedly resulted in bis(1*H*-tetrazol-5-yl)furoxan diammonium salt **4e**. First, we isolated the final product **2e** by acidification of the reaction mixture with 10% HCl followed by extraction with ether (Table 2, entries 8–10). However, subsequent screening showed that the primary isolation of salt **4e** is preferable for higher yield of the final product. The optimal conditions for its preparation include application of $TMSN_3$ excess (5 mol) and 2 mol of $NH_4F$ per mole of initial dinitrile **1e** in MeCN at 20 °C. Under these conditions, the reaction is completed in 24 h affording the required salt **4e** in good yield (Table 2, entry 12). An increase in the $TMSN_3$/dinitrile **1e** molar ratio to 10:1 did not provide a higher yield (Table 2, entry 13).

The selected optimal conditions proved to be suitable for the transformation of other cyanofuroxans **1** (except 3-cyano-4-nitrofuroxan **1f**) to the corresponding mono- and diammonium