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Highly regio- and stereoselective 1,3-dipolar cycloaddition of stabilised azomethine ylides to 3,3,3-trihalogeno-1-nitropropenes: Synthesis of trihalomethylated spiroindenepyrroli(zi)dines

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ABSTRACT

Reactions of (*E*)-3,3,3-trihalogeno-1-nitropropenes with stabilised azomethine ylides derived from ninhydrin and indenoquinoxalinones on the one hand, and sarcosine and proline on the other, proceed regio- and diastereoselectively to give a number of trihalomethylated spiroindenepyrrolidines and spiroindenepyrrolizidines in good yields.

1. Introduction

The introduction of a trihalomethyl group, especially a trifluoromethyl group, in organic molecules is an important synthetic task since the resulting compounds possess a wide range of useful properties and are of great interest for pharmacy and agrochemistry [1]. The importance of a trifluoromethyl group among several types of alkyl and haloalkyl moieties was observed in many therapeutic medicines [2]. However, despite the biological and chemical potential of CF_3-containing heterocyclic compounds, the regio- and stereoselective synthesis of these molecules from readily available synthons remains a challenge. Previously, the stereoselective syntheses of trifluoromethylated pyrrolidines and pyrrolizidines via the 1,3-dipolar cycloaddition of non-fluorinated azomethine ylides with CF_3-containing alkenes and alkynes or CF_3-containing azomethine ylides with non-fluorinated alkenes were reported . For example, 1-trifluoromethylated pyrrolizidines were obtained in moderate yields and excellent diastereoselectivity by the reaction with β-trifluoromethyl acrylamides and azomethine ylides generated from proline and several aldehydes [3a]. On the other hand, while the reactions of unactivated alkenes, chalcones and β-nitrostyrenes with stabilised azomethine ylides were studied thoroughly [4], very little information is available on the stereoselective [3 + 2] cycloaddition reaction of azomethine ylides with CX_3-substituted nitroalkenes (X = F, Cl, Br).

At the same time, we envisaged that introduction of such powerful electron-withdrawing substituents like CF_3, CCl_3 and CBr_3 groups into the conjugated nitroalkene moiety would increase their reactivity toward 1,3-dipolar cycloaddition with azomethine ylides and open a new synthetic use of these small molecules. Indeed, we have recently reported a convenient method for the synthesis of trihalomethylated spiro[indoline-3,2′-pyrrolidin]-2-ones and spiro[indoline-3,3′-pyrrolizin]-2-ones via the 1,3-dipolar cycloaddition of azomethine ylides generated from decarboxylative condensation of isatins and *N*-alkyl-α-amino acids (sarcosine and proline) with (*E*)-3,3,3-trihalogeno-1-nitropropenes [5].

In the present paper, we focused on the unique electronic and steric properties of trihalomethylated nitroolefins and report that these compounds are good dipolarophiles toward stabilised azomethine ylides derived from ninhydrin and indenoquinoxalinones on the one hand, and sarcosine and proline on the other hand. These reactions provide a simple and efficient synthetic route to CX_3- and NO_2-containing spiroindenepyrrolidines and spiroindenepyrrolizidines, the regio- and stereochemistry of which, as well as all by-products, has been established by 1D and 2D NMR spectroscopy and X-ray diffraction analysis. It is important that the major products of the reaction with proline ylides showed different regioselectivity from the reported spiropyrrolizidines, prepared from β-nitrostyrenes [4e–j].

2. Results and discussion

In connection with our interest in the chemistry of trihalomethylated nitroolefins [5,6], which are easily obtained from nitromethane and trihaloacetaldehydes [7,8], we decided to study the reactions of

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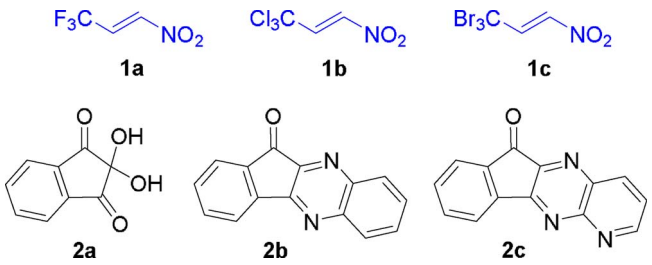


Fig. 1. Nitroalkenes **1a–c** and indenes **2a–c** used in this study.

(*E*)-3,3,3-trihalogeno-1-nitropropenes **1a–c** with a set of stabilised azomethine ylides generated from decarboxylative condensation of ninhydrin **2a** and indenoquinoxalinones **2b,c** with *N*-alkyl-α-amino acids such as sarcosine and proline (Fig. 1).

In the initial study, we have developed the synthesis of the hitherto unknown spiroindenepyrrolidines **3a–c** starting from CX_3-nitropropenes **1a–c**, ninhydrin **2a** and sarcosine by a one-pot, three-component procedure depicted in Scheme 1. We have found that these reactants in benzene at 35 °C for 4 h resulted in the formation of cycloadducts **3a–c** in 63–81% (X = F, Cl) and 37% (X = Br) yields as single isomers with *trans*-configuration of the CX_3 and NO_2 groups due to the synchronism of the reaction, the structures of which were fully characterized by spectroscopic methods and X-ray diffraction analysis (Fig. 2). The progress of the reaction was monitored by TLC, and the results are summarised in Table 1. Among various solvents with different polarities (benzene, toluene, acetonitrile, isopropanol, dioxane, *tert*-butyl methyl ether, THF, DMSO, DMF), which have been tested to perform the reaction, benzene was identified as the best solvent in terms of yield and selectivity.

When proline was used as an α-amino acid, the desired spiroindenepyrrolizidines **4a–c** were obtained as *endo*-adducts (with respect to NO_2) under the same conditions at room temperature in moderate (48%) to very high yields (79–94%), depending on the steric properties of the trihalomethyl group (Scheme 1, Table 1). Thus, the cycloaddition proceeds in a high regio- and stereocontrolled fashion, however, in the case of more reactive CF_3-nitropropene 1a, product **4a** was isolated as a mixture of two regioisomers in the ratio of **4a**:**4'a** = 84:16, from which isomer **4a** was obtained as a single crystal for X-ray diffraction analysis (Fig. 3). All compounds **3** and **4** were isolated as yellow powders.

The above results encouraged us to extend this methodology to

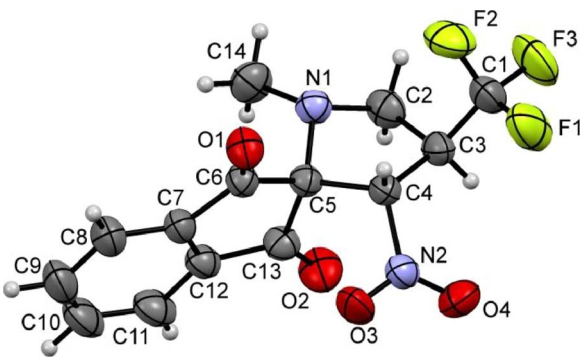
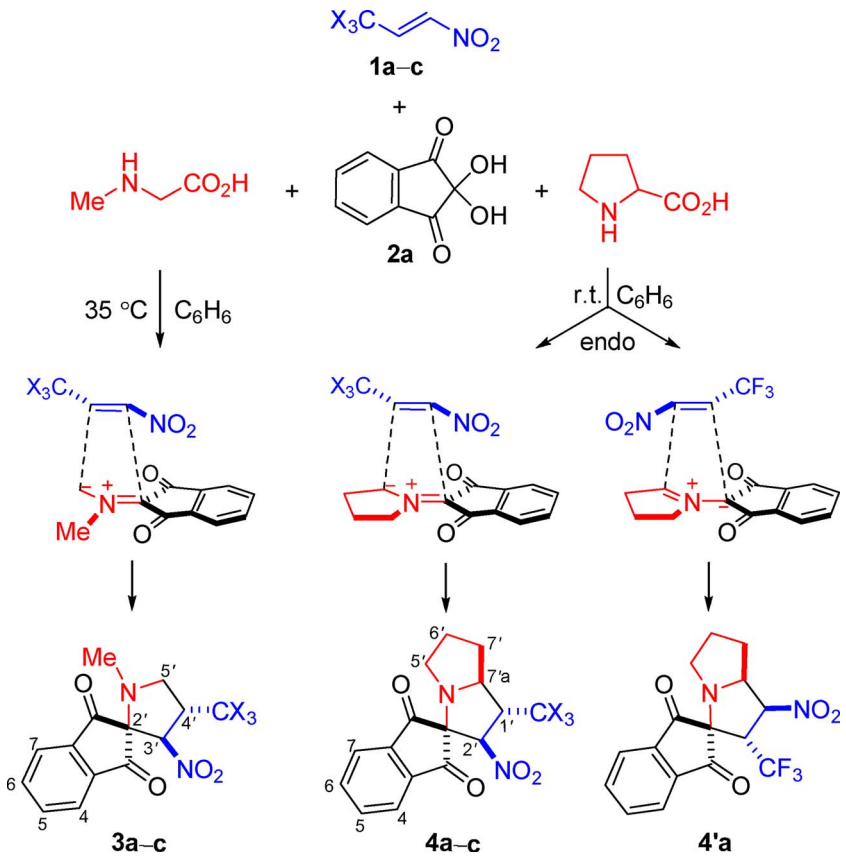


Fig. 2. X-ray crystal structure of **3a** (ORTEP drawing, 50% probability level).

Table 1
Isolated yields of compounds **3a–c** and **4a–c** (all structures are racemic).

Nitropropene **1**	X	Adduct	Yield (%)	Adduct	Yield (%)
1a	F	**3a**	81	**4a**[a]	94
1b	Cl	**3b**	63	**4b**	79
1c	Br	**3c**	37	**4c**	48

[a] As a mixture of **4a**:**4'a** = 84:16.



Scheme 1. Synthesis of compounds **3a–c** and **4a–c** by the reaction of nitroalkenes **1a–c** with ninhydrin–sarcosine/proline ylides (*endo*-adducts with respect to NO_2).