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Synthesis of poly-functionalized pyrazoles and pyridazines from nitrobutadienes: an interesting dichotomy of practical relevance

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ABSTRACT

The initial ring-opening of 3-nitrothiophene and further structural modifications lead to nitrobutadienic building-blocks whose synthetic usefulness in the field of heterocycles has been widely demonstrated. As a further example, the Michael addition of a hydrazone anion to the nitrovinyl moiety of nitrobutadienes generates 1,2-diazaheterocycles as the final result of an overall MIRC process. Depending on the nature of the substituents on the Michael-type acceptor and on the hydrazono nucleophile, an interesting dichotomy is observed that leads to either five-member or six-member N-heterocycles with complete selectivity. The results obtained appear to be both of mechanistic and synthetic interest e.g., in the field of heterocycles endowed with potential pharmacological/biological activity.

1. Introduction

The synthesis of N-heterocycles is a goal of utmost importance in organic, bioorganic and pharmaceutical chemistry,[1] and the intermediacy of conjugated nitrodienes has been recently reviewed.[2] In this field, over the last two decades our research group has provided a valuable contribution thanks to the versatility of building-blocks such as **4**–**11** (Scheme 1). Such poly-functionalized units, most conveniently obtainable from the initial ring-opening of suitably-substituted nitrothiophenes with secondary amines,[3–5] followed by modifications of the original functionalities so as to meet specific requirements, both structural and electronic (Scheme 1), exhibit a multi-faceted behaviour:[6] this obviously encompasses the well-known reactivity of e.g., nitrovinyl, nitroenaminic, sulfonylvinyl systems.[7] Accordingly, the nitrobutadienes reported in Scheme 1 have provided sulfur, oxygen and/or nitrogen atoms for the construction of a number of different heterocycles in an overall ring-opening/ring-closing protocol characterized by a high atom economy.[8]

More recently, the construction of poly-functionalized heterocycles has been successfully performed by means of an initial Michael-type addition onto the nitrovinylic moiety of nitrobutadienes,[8a,d–h] a synthetic approach sometimes indicated as a Michael addition Induced Ring Closure (MIRC) process.[9]

In this line, preliminary results[10] on the reaction between the model nitrobutadienes **12a** and **13a** (Scheme 1, Ar=*p*-Tol, X=Y=H in **7** and **8**, respectively), purposely chosen in order to provide two significantly different electronic distribution patterns on the diene moiety, and the anions of hydrazones **14a**–**d**, have enlightened the possibility to apply the initial Michael-type addition strategy also to the preparation of heterocycles containing two adjacent nitrogen atoms (cf. Scheme 2). Actually, with the exception of some pyrazolines,[6b] similar structures were still lacking in our expanding 'pool' although pyrazoles, in particular, surely represent appealing targets: the wide range of biological and pharmacological activities displayed by such molecules (among which: anti-hyperglycemic, anti-inflammatory, anti-obesity, or antitumoral[11]) accounts for the impressive amount of literature, which continuously deals with relevant synthetic or applicative aspects.[12]

On the grounds of the preliminary results, it seemed therefore worthwhile to fully investigate the behaviour of nitrobutadienes **13** in order to better define the scope of the access to highly-functionalized pyrazoles or pyridazines such as **16** or **17**, respectively, and also to gain more information on the origin of the dichotomic behaviour that generates different N-heterocyclic structures. Relevant results are reported hereinafter.

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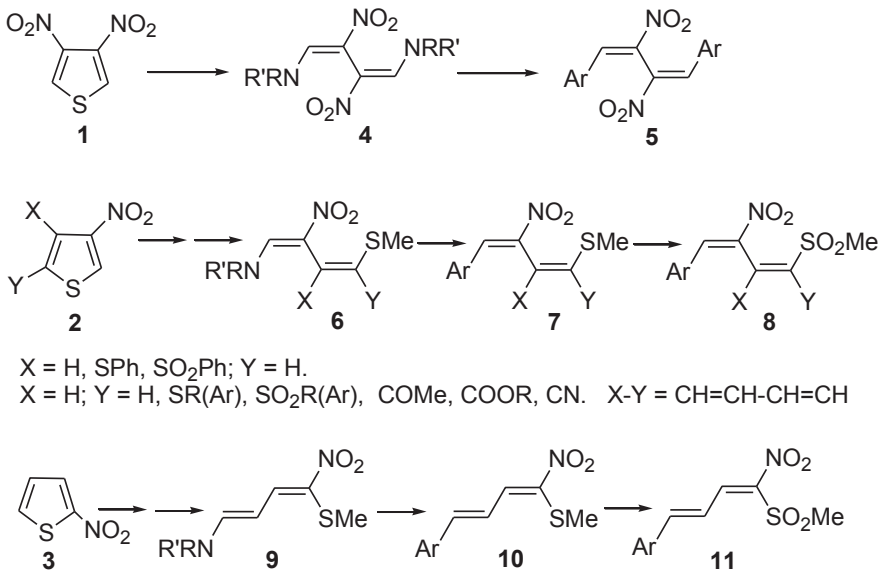
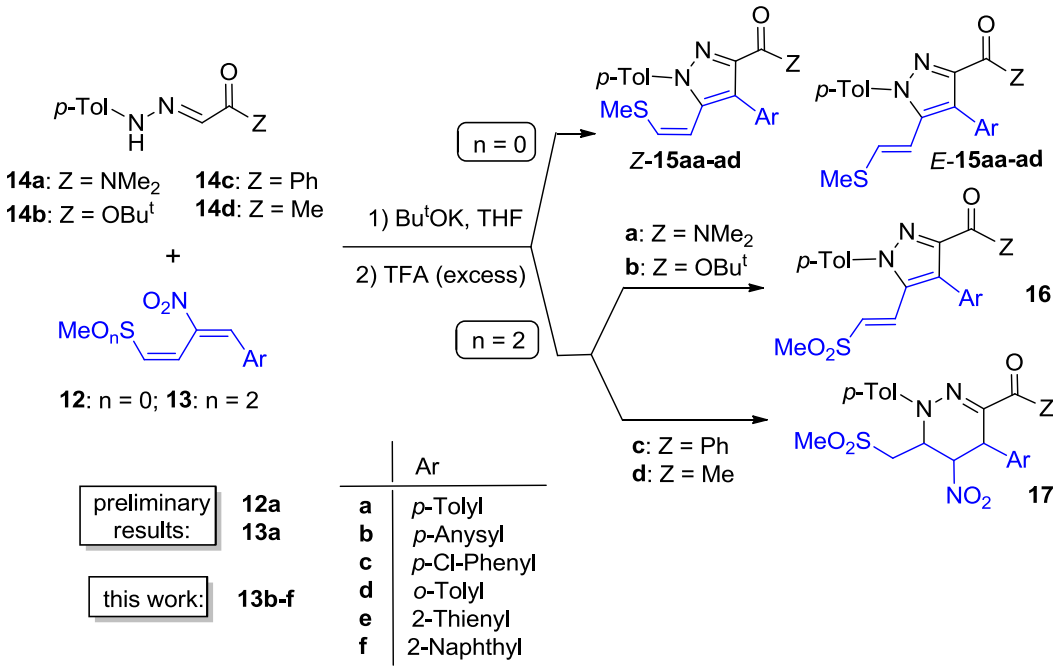


Scheme 1. Nitrobutadienic building-blocks from the initial ring-opening of nitrothiophenes **1**–**3**.



Scheme 2. Pyrazoles **15** and **16**, and tetrahydropyridazines **17** from the reaction between **12a** and **13a**–**g** with the anions of α-oxohydrazones **14a**–**d**. Data for **12a** and **13a** are from a preliminary communication.[10]

2. Results and discussion

2.1. Dichotomic behaviour of nitrosulfonylbutadienes 13

As shown in Scheme 2, the behaviour of nitrobutadienes **12a** and **13a** towards the anions (generated with Bu^{t}OK) of hydrazones **14a**–**d** in THF at −78 °C turns out to be markedly different. On one side, sulfide **12a** effectively builds-up a pyrazole nucleus independently of the nature of Z in the employed hydrazone, with a partial inversion of the exocyclic C=C double-bond configuration.[10]

Much more interestingly, depending on the nature of *Z*, sulfone **13a** produces two different heterocycles. The latter reaction was therefore considered to deserve a deeper insight and was first of all extended to other substrates with different Ar moieties. The results obtained by treatment of nitrobutadienes **13b**–**f** with the α-oxohydrazones **14a**–**d** (Scheme 2, Tables 1 and 2) cleanly line-up with the preliminary ones for the model *p*-tolyl derivative **13a**: whichever the nature of Ar, hydrazones **14a**,**b** (*Z*=NMe$_2$ and OBu^t, respectively) exclusively furnish the tetra-substituted pyrazoles **16** (Table 1), while **14c**,**d** (*Z*=Ph and Me, respectively) exclusively lead to the likewise fully-substituted tetrahydropyridazines **17** (Table 2).