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An efficient synthesis of multisubstituted 4-nitrobuta-1,3-dien-1-amines and application in cyclisation reactions

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ABSTRACT

The synthesis of multisubstituted 4-nitrobuta-1,3-dien-1-amines (nitrodienamines) from 3-aminocrotonates and nitroacetaldehyde potassium salt, has been performed in 45–89% yields. This one-step protocol works efficiently with a broad range of N-H and N-substituted 3-aminocrotonates and delivers both primary and secondary nitrodienamines. In addition, the possible variations of the substituents at the positions 2 and 3 of 4-nitrobuta-1,3-dien-1-amine have been shown. Generally, the yields of secondary 4-nitrobuta-1,3-dien-1-amines were lower than those of primary ones. The synthetic usefulness of obtained 4-nitrobuta-1,3-dien-1-amines has also been demonstrated by achieving the synthesis of multisubstituted 5-nitro-1,6-dihydropyridines in two-component cyclocondensation reactions of 4-nitrobuta-1,3-dien-1-amines with aromatic or aliphatic aldehydes. Lastly, diverse N-H and N-substituted 5-nitro-1,6-dihydropyridines have been obtained in 35–87% yields.

1. Introduction

Dienamines are important synthons for construction of various heterocyclic systems. They are also known as key intermediates in Bohlmann-Rahtz pyridine synthesis[1,2] which is a useful two-step method to access di- and trisubstituted pyridines. The applications of the original procedure now have been broadened by using both metal-based or metal-free Lewis acids and Brønsted acid catalysis.[3] Furthermore, the method is extended with NBS-mediated bromocyclisation of dienamines providing various target molecules.[4]

Nitrodienamines may become useful synthons in organic synthesis due to the enaminic, dienic, and electronic push-pull character of these molecules.[5,6] Although much progress has been made in the field of nitrodienamines in past decades, efficient synthesis of primary and secondary nitroenamines remains underdeveloped, and their chemistry has been scarcely investigated. Synthetically, nitrodienamines can be approached by several multistep methodologies.[5–12] Thus, the reaction of acetaldehydes with 1-dimethylamino-2-nitroethylene followed by treatment of the resulting condensation product with pyrrolidinium acetate afforded *tert*-nitrodienamines, with terminal pyrrolidine groups.[7] Synthesis of *sec*-nitrodienamines previously was also performed *via* two methodologically similar multistep procedures (Scheme 1, Pathways A,B). Specifically, the reaction of 3-(dimethylamino) acrolein with dimethylamine followed by a treatment of formed salt with nitromethane gave 1-(N,N-dimethylamino)-4-nitro-1,3-butadiene (*tert*-nitrodienamine) (Scheme 1 Pathway A).[5,6,8] Alternatively, the reaction of methylsulfate salt of 3-(dimethylamino) acrolein with nitromethane or nitroethane also offered *tert*-nitrodienamines (Scheme 1 Pathway B).[9] The resulting *tert*-nitrodienamines further can be converted to *sec*-nitrodienamines by reaction with primary amines.[5,6]

Cyclisation of *sec*-nitrodienamines with aldehydes offered various N-substituted 2-methyl-3-nitro-1,2-dihydropyridines (Scheme 1, Pathways A,B).[5] The nitroalkenylation reactions of 2-methylindolines with nitroenamines afforded nitrodienamine derivatives in which the amino group was encrypted in the dihydroindole cycle.[10] Nitrobutadiene derivatives having pyrrolidinyl terminal substituents were also obtained *via* ring opening reactions of 2-nitrothiophene with

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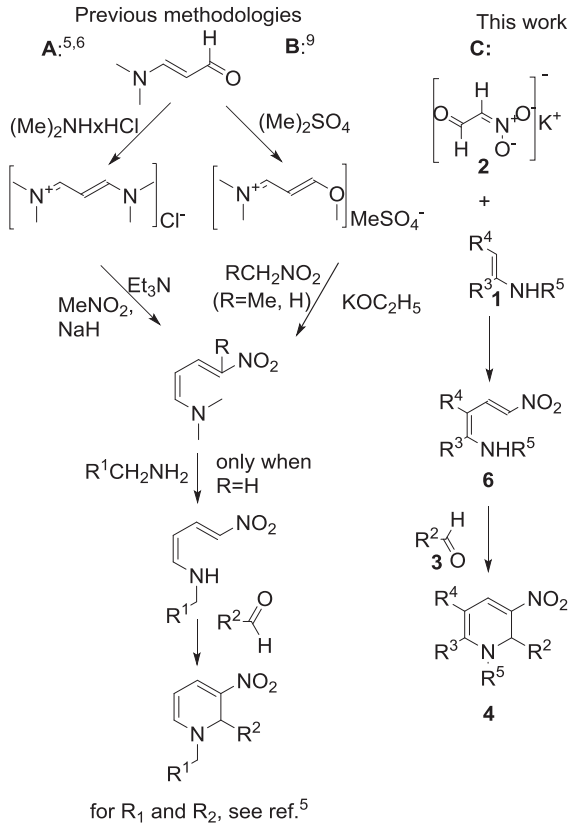


Scheme 1. Synthesis of nitrodienamines using three different techniques: application to the synthesis of dihydropyridines.

secondary amines.[11] The only methodology providing primary nitrodienamines (3-amino-3-dialkylaminopropenenitriles) is based on the reaction of nitroketene dithioacetal and enaminonitriles.[12] The resulting nitroenamine in reaction with orthoformate or acetic anhydride provided the corresponding highly functionalised pyridines.

The previous synthesis of 2-aryl-3,5-dinitro-1,2-dihydropyridines was conducted in an unusual condensation of nitroacetaldehyde with paraformaldehyde or aromatic aldehydes and ammonium acetate in acetic acid.[13] The change of the reaction medium to a mixture of ethanol/acetic acid led to the formation of 1,2-dihydropyridine (1,2-DHP) with 1,4-dihydropyridine (1,4-DHP) as a minor reaction product.

The synthesis of 3-nitro substituted 1,4-DHPs usually is performed in two component cyclisations starting from nitroenamines and arylidene acetoacetates.[13–15] Electron spin resonance (ESR) studies of few 2,5,6-trisubstituted 5-nitro-1,6-DHPs have been already published by Baumane et al.[16,17] However, the details of the synthesis and the physico-chemical characterisation of these compounds were not included in the articles. The limited availability of synthetic methods for the preparation of 1,2-dihydropyridines of which many are pharmacologically important led to considerable efforts toward the development of new and efficient methodologies for the synthesis of 1,2-dihydropyridines.[18] However, to the best of our knowledge, the synthesis of unsymmetrical multisubstituted 5-nitro-1,6-DHPs has not been well developed.

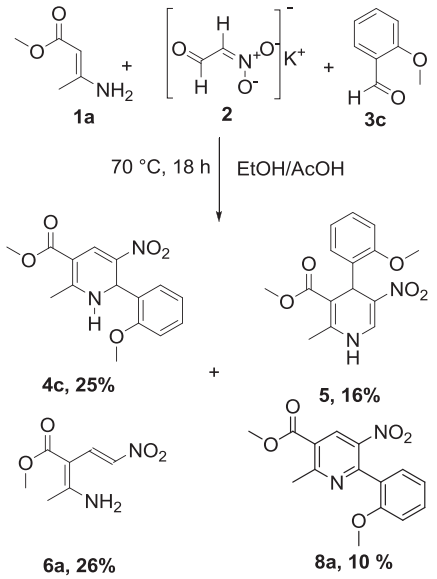
This paper describes the synthesis of novel primary and secondary nitrodienamines from 3-aminocrotonates and nitroacetaldehyde potassium salt (Scheme 1 Pathway C). The usefulness of obtained nitrodienamines was shown by the synthesis of multisubstituted 5-nitro-1,6-dihydropyridines in the two-component cyclocondensation reaction of nitrodienamines with aromatic or aliphatic aldehydes. Thus, this paper reports the synthesis of multisubstituted 5-nitro-1,6-dihydropyridines for the first time.

2. Results and discussion

The first attempt to synthesise 5-nitro-1,6-DHP-3-carboxylates was based on Hantzsch type cyclisation of 3-aminocrotonates **1**, nitroacetaldehyde potassium salt (**2**) and aromatic aldehydes **3** (Scheme 2). This reaction leads to the formation of multiple products in low yields, making this approach unpractical.

Thus, the reaction of methyl 3-aminocrotonate (**1a**), nitroacetaldehyde potassium salt (**2**) and 2-methoxybenzaldehyde (**3c**) was performed in a mixture of ethanol and acetic acid that was heated overnight at 70 °C (Scheme 2). Major components of the complex reaction mixture were 1,6-DHP **4c**, 1,4-dihydropyridine **5**, nitrodienamine **6a** and the oxidation product of **4c** - pyridine **8a**. Nitrodienamine **6a** was obtained unintentionally to synthesise 1,6-DHP **4c**. Structurally, the isolated nitrodienamine **6a** in reaction with aldehydes could furnish 1,6-DHP cycle. The major drawback of this reaction is the formation of various products. Consequently, a more efficient method is needed, and the application of nitrodienamines seems to be promising for the synthesis of 5-nitro-1,6-DHPs **4a-t**.

The second approach consisted of two steps; the first step involved facile synthesis of novel nitrodienamine derivatives **6a-o** from the appropriate 3-aminocrotonates **1a-o**[19–22] and nitroacetaldehyde potassium salt (**2**) in a mixture of methanol and acetic acid at room temperature under argon atmosphere for 24 h in 45–89% yields (Table 1). Nitroacetaldehyde potassium salt (**2**) was obtained according to the literature[23,24] in the reaction of nitromethane, triethyl orthoformate and methylphenyl amine *via* formation of 2-nitroenamine derivative followed by treatment with potassium hydroxide. The reaction medium contained acetic acid to liberate nitroacetaldehyde from its potassium salt. This method appeared to be very versatile, allowing the synthesis of both primary and secondary nitrodienamines **6a-o** with different substituents at the positions 2 and 3. These nitrodienamines **6a-e,h,l-o** were then further used to obtain N-H and N-substituted 1,6-DHPs



Scheme 2. Cyclisation of methyl 3-aminocrotonate (**1a**), nitroacetaldehyde potassium salt (**2**) and 2-methoxybenzaldehyde (**3c**). Reaction conditions: **1a** (10 mmol), **2** (12 mmol) and **3c** (10 mmol).