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Reinvestigations into synthesis of allyldithiocarbamates and their intramolecular cyclization: synthesis and antihyperglycemic activity of 2-thioxothiazolidine-4-alkanoates

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ABSTRACT

Reinvestigating the synthesis of allylthiocarbamates from MBH derivatives revealed that they are obtained more efficiently from allylbromides in isopropanol rather than acetates in water. Further unlike reported, the base-mediated intramolecular cyclization of these allyldithiocarbamates give substituted 2-thioxothiazolidine-4-alkanoates instead of substituted 1,3-thiazines and the reaction was restricted to 2- or 4-nitrophenyl carrying substrates. Screening of these products for antihyperglycemic activity revealed that **5bC** displays significant activity via partial agonist activity on PPARγ at transcriptional level, which was corroborated by molecular docking studies.

1. Introduction

Over last several years we have been actively exploring the utility of Morita–Baylis–Hillman (MBH) chemistry[1] for the synthesis of heterocyclic scaffolds endowed with biological properties.[2] In this context in one of our works we have achieved the synthesis of 5,6-dihydro-4*H*-1,3-thiazines from allylamine obtained from MBH adduct.[3] Notably the 1,3-thiazine core is represented in cephalosporin class of antibiotics. Prior to our work Yadav et al. have reported the synthesis of 3,5-dibenzyl-1,3-thiazines via base-mediated intramolecular cyclization of allyldithiocarbamates, which in turn were prepared from the MBH acetates in water (Fig. 1).[4] In one of our research programs we need to synthesize identical allyldithiocarbamates. However we discovered that the reaction of MBH acetate **2a** obtained from MBH adduct (**1a**) of benzaldehyde and methyl acrylate with dithiocarbamate **A** (prepared from CS_2 and benzylamine) in water as medium was unsuccessful. A careful literature survey revealed that Jacobine and

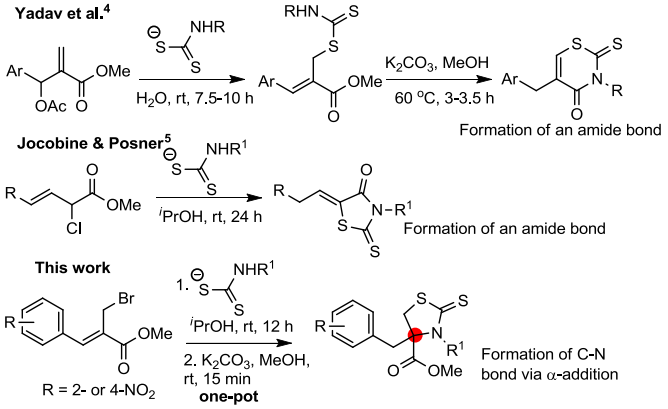

Fig. 1. Synthesis of thioaza heterocycles from reaction of allylic substrates with thiocarbamate.

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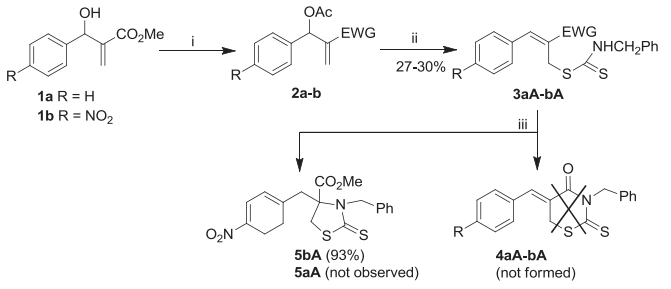
Posner reported S_N2-displacement of allylic chloride with in situ generated dithiocarbamate for the synthesis of 2-thioxo-1,3-thiazolidine-4-one in isopropanol.[5] Taking a cue from this report, we treated **2a** with dithiocarbamate **A** in isopropanol as the medium. We observed that though the reaction was now successful, allyldithiocarbamate **3aA** was isolated in 27% yield only. Another MBH acetate **2b** derived from MBH adduct (**1b**) of 4-nitrobenzaldehyde under identical reaction conditions furnished the corresponding allylthiocarbamate **3bA** in 30% yield. Further probe into the base-mediated intramolecular cyclization revealed that whereas the reaction of **3aA** to furnish **4aA** failed, reaction of **3bA** was completed in 15 min to yield methyl 3-benzyl-4-((4-nitrocyclohexa-1,3-dien-1-yl)methyl)-2-thioxothiazolidine-4-carboxylate (**5bA**) instead of the expected **4bA** (Scheme 1). It is worth mentioning that 1,3-thiazolidine-2-thione core is of significant medicinal interest as it is well represented in several compounds endowed with a variety of bioactivities.[6] In addition, derivatives of 1,3-thiazolidine-2-thione are present in chiral auxiliary employed for asymmetric synthesis and additives for the photographic fixing materials.[7] Although Li et al.[8] and later Emami et al.[9] disclosed one-pot synthesis of 1,3-thiozolidine-2-thiones via reaction of primary amines with carbon disulfide and ethyl 3-bromo-2-oxopropanoate or phenacyl bromide, most of the earlier approaches were multistep process involving harsh conditions. The formation of the product **5bA** could be attributed to α-addition of nucleophile in cinnamates bearing strong electron withdrawing group on the phenyl ring. In view of the ambiguous findings, we considered reinvestigating the formation of allylthiocarbamate from MBH adducts and their base-mediated intramolecular cyclization in greater details. Additionally we became interested to assess the possibility of α-addition of amines in substituted nitrocinnamates generated from MBH adducts as it would allow easy access to α-quaternary α-amino acids. In order to find end use of the products obtained during the study, the library of substituted 2-thioxothiazolidine-4-alkanoates was evaluated for anti-hyperglycemic activity where one of the analogues was found to display promising activity. Herein we report the results of our study toward one-pot synthesis and antihyperglycemic activity of 2-thioxothiazolidine-4-alkanoates.



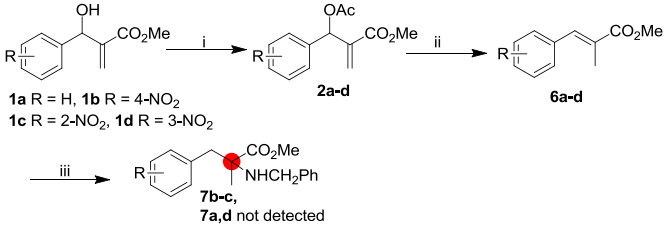
Scheme 1. Reagents and conditions: (i) AcCl, Py, CH_2Cl_2, 0 °C to rt, 3 h; (ii) CS_2, $PhCH_2NH_2$ (**A**), ^iPrOH, rt, 12 h; (iii) K_2CO_3, MeOH, rt, 15 min.

2. Results and discussion

2.1. Chemistry

As indicated in the preceding text we initiated our study by performing the reaction of MBH acetates **2a**,**b** with dithiocarbamate **A** in isopropanol to successfully prepare the corresponding allyldithiocarbamates **3aA**,**bA**, albeit in low yields only. In contrast to the findings of Yadav et al., we discovered that treating **3aA**,**bA** with K_2CO_3 in methanol resulted completion of reaction for **3bA** in 15 min to afford a product in 93% yield but **3aA** was recovered unreacted even after 24 h or heating for prolonged time. A detailed spectroscopic analysis of the product delineated its structure as **5bA** (Scheme 1). The formation of **5bA** is rationalized on the basis of α-addition of nucleophile in nitrocinnamates, which has literature precedence. Lewandowska et al. and Chatfield et al. earlier reported that presence of two nitro groups or one nitro and a trifluoromethyl group on a phenyl ring attached to carbon-β redirects the regioselectivity of nucleophilic addition from the classical β-addition to an abnormal α-addition in cinnamaldehyde or cinnamic esters.[10,11] From the theoretical studies, this inversion was attributed to decrease in the reaction barrier of α- versus β-addition due to increase in electron withdrawing character on the β-carbon.

Mechanistic considerations invoked us to study the fate of nucleophilic addition of amines in nitrocinnamates, which could be readily prepared from the MBH adducts. A successful α-addition in substituted 3-(nitrophenyl)-2-alkenoates (nitrocinnamates) would provide easy access to α-quaternary α-amino acids (substituted *tert*-alkylamines), which are of immense interest due to their presence in natural products and bioactive agents.[12] In this context therefore (*E*)-methyl 2-methyl-3-(4-substitutedphenyl)acrylates **6a**–**d** were prepared from the MBH adducts **1a**–**d** following the reported procedure.[13] These compounds were treated with benzylamine in the presence of NaH using THF as the medium (Scheme 2). Whereas **6b** and **6c** successfully underwent reaction to afford the corresponding α-products **7b** and **7c** in good yields, compounds **6a** and **6d** failed to undergo the reaction. This result inferred that perhaps the presence of 2-nitro or 4-nitro group on the phenyl ring is essentially required for a successful α-addition of nucleophiles in MBH adduct. However, unlike earlier reports[10,11] the presence of an additional nitro or trifluoromethyl group in the phenyl ring in 2-nitrocinnamates is not necessary for the α-addition of amines to yield α-quaternary α-amino acids.



Scheme 2. Reagents and conditions: (i) AcCl, Py, CH_2Cl_2, 0 °C to rt, 3 h; (ii) $NaBH_4$, MeOH, rt, 30 min; (iii) NaH, $PhCH_2NH_2$, 0 °C to rt, 3 h.

The successful α-addition of amines to the MBH derivatives **6b**,**c** validated the basis for the formation of the substituted thioxothiazolidine-4-carboxylate. Therefore the next objective of the study was to improve upon the yields of the allylthiocarbamates. It is known that the allyl bromide, which can be readily prepared from the MBH adduct is a better substrate than the MBH acetates for the addition reactions. Therefore, we prepared the allyl bromide **8b** from the adduct **1b** following the reported procedure.[2h,14] The reaction of **8b** with the in situ generated dithiocarbamate **A** (from CS_2 and benzylamine) in isopropanol as medium was successful to afford the allyldithiocarbamate **3bA** in 95% yield (Scheme 3). More importantly the work up of this reaction involved a simple filtration to isolate the required product. At this stage we explored the possibility of performing the reaction sequence (**8b** to **3bA** to **5bA**) as a one-pot protocol using methanol as the medium, but the one-pot reaction gave **5bA** in 48% yield only. Nevertheless, to accomplish the sequence as a one-pot protocol, the allyldithiocarbamate **3bA** was prepared from **8b** in isopropanol followed by removal of solvent and continuation of the reaction with the addition of K_2CO_3 in methanol. It was pleasing to note that this procedure gave **5bA** in comparable yield to the one obtained via the two-step process. Next we prepared the allylbromides **8a**,**c**,**d** from corresponding MBH adducts **1a**,**c**,**d** and subjected them to addition reaction with the dithiocarbamate **A**. All reactions were successful to furnish the