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Reactivity of sarcosine and 1,3-thiazolidine-4-carboxylic acid towards salicylaldehyde-derived alkynes and allenes

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ABSTRACT

The reaction of sarcosine and 1,3-thiazolidine-4-carboxylic acid with salicylaldehyde-derived alkynes and allenes opened the way to new chromeno[4,3-*b*]pyrrole and chromeno[2,3-*b*]pyrrole derivatives. Tetrahydro-chromeno[4,3-*b*]pyrroles were obtained from the reaction of these secondary amino acids with *O*-propargylsalicylaldehyde. Interestingly, sarcosine reacted with ethyl 4-(2-formylphenoxy)but-2-ynoate to give a monocyclic pyrrole resulting from rearrangement of the initially formed 1,3-dipolar cycloadduct. Decarboxylative condensation of ethyl 4-(2-formylphenoxy)but-2-ynoate with 1,3-thiazolidine-4-carboxylic acid afforded in a stereoselective fashion the expected chromeno-pyrrolo [1,2-*c*]thiazole, which structure was unambiguously established by X-ray crystallography. However, the 1*H*,3*H*-pyrrolo[1,2-*c*]thiazole resulting from the opening of the pyran ring was also isolated. The reaction with *O*-buta-2,3-dienyl salicylaldehyde afforded 3-methylene-hexahydrochromeno[4,3-*b*]pyrrole. *O*-Allenyl salicylaldehyde reacted with sarcosine and 1,3-thiazolidine-4-carboxylic acid to give a new type of chromeno-pyrroles. A mechanism proposal for the synthesis of these chromeno[2,3-*b*]pyrroles has been presented.

1. Introduction

Chromene and chromane substructures are frequently found in naturally occurring compounds, many of which exhibit useful biological activity.[1] This led to the search for new compounds inspired on these structural motifs in order to obtain molecules with relevance in medicinal chemistry. In this context, hetero-annulated chromene and chromane derivatives, namely chromeno[4,3-*b*] pyrrole derivatives, are important target molecules. Reports on the construction of the chromeno[4,3-*b*]pyrrole ring system include the condensation of alkenyl and alkynyl ethers of salicylaldehydes with either α-amino acid esters or secondary amino acids followed by intramolecular 1,3-dipolar cycloaddition of the in situ generated azomethine ylides.[2] Intramolecular cycloaddition of mesoionic 2-[2-(prop-2-ynyloxy)phenyl]oxazolium-5-olates prepared from the corresponding *N*-acylamino acids is an alternative approach to chromeno[4,3-*b*]pyrroles.[3] 2-Fluorochromeno[4,3-*b*]pyrroles have also been prepared by intramolecular cycloaddition of azomethine ylides generated from the reaction of difluorocarbenes with imines derived from alkenyl and alkynyl ethers of salicylaldehydes.[4] A similar approach involving the generation of azomethine ylides from ethoxycarbonylcarbenoids and Schiff bases of *O*-alkynyl salicylaldehydes is known.[5] On the other hand, it has been demonstrated that the reaction of imines derived from *O*-alkenyl salicylaldehydes and acid chlorides mediated by PhP(2-catechyl) leads to chromeno[4,3-*b*]pyrrole derivatives via intramolecular cycloaddition of phosphorus-containing 1,3-dipoles.[6]

Despite the existing methods for the synthesis of chromeno[4,3-*b*]pyrrole derivatives, there still is demand for strategies to achieve wider structural diversity. Our approach was to study the reactivity of sarcosine and 1,3-thiazolidine-4-carboxylic acid with a variety of salicylaldehydes bearing internal dipolarophiles, including derivatives with an allenic moiety, which could give access to new types of tetrahydrochromeno-pyrrole derivatives.

2. Results and discussion

O-Propargylsalicylaldehyde (**2**) was efficiently obtained from the reaction of salicylaldehyde with propargyl bromine in refluxing ethanol in the presence of potassium carbonate. The Crabbé homologation of terminal alkynes was applied to the synthesis of *O*-buta-2,3-dienyl salicylaldehyde (**3**).[7] Thus, the copper(I) bromide mediated reaction of salicylaldehyde **2** with formaldehyde and *N*,*N*′-diisopropylamine in refluxing dioxane afforded the corresponding allenic derivative **3** in 70% yield. The protection of the aldehyde functionality of compound **2** was achieved by treatment

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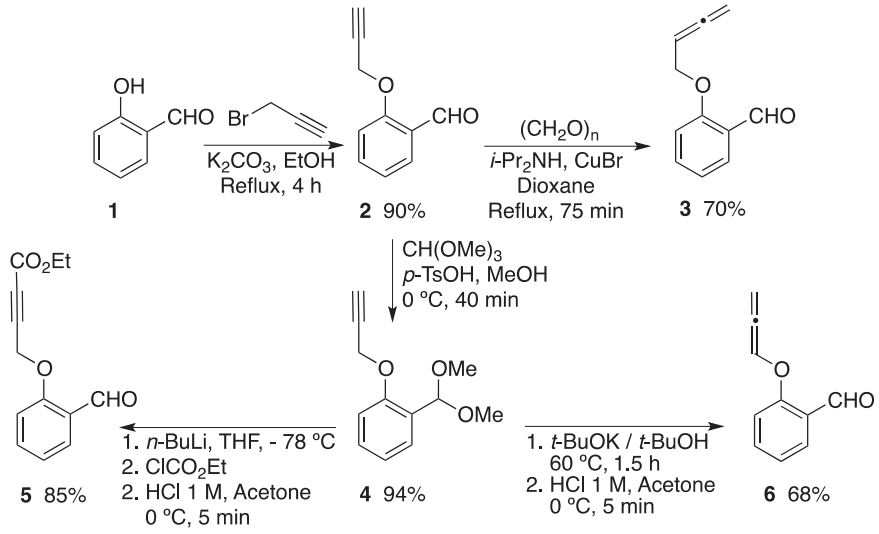
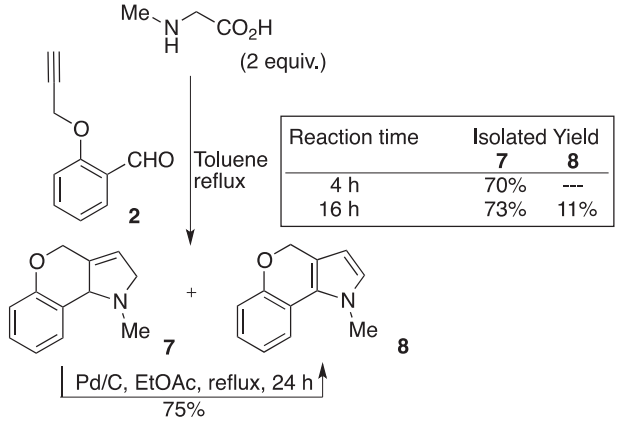
with a 5:1 methanol–trimethyl orthoformate solution in the presence of *p*-toluenesulfonic acid following previously reported general procedures.[8] The acetal protected salicylaldehyde **4** reacted with potassium *tert*-butoxide in *tert*-butanol at 60 °C to give the aryloxyallene derivative after 1.5 h, as described for other aryl propargyl ethers.[9] The acetal group was smoothly hydrolyzed with 1 M HCl to afford *O*-allenyl salicylaldehyde (**6**) in good yield.[8a] Attempts to prepare aldehyde **6** from *O*-propargylsalicylaldehyde (**2**) without resorting to aldehyde protection, following a reported methodology,[10] were not successful. The functionalization of terminal alkyne **4** with a carboxylate group was carried out by reacting it with butyllithium followed by the reaction with ethyl chloroformate.[11] Deprotection[8a] of the acetal group gave the target *O*-propargylsalicylaldehyde **5** in 85% overall yield (Scheme 1).

Initially, we looked again into the reaction of *O*-propargylsalicylaldehyde (**2**) with sarcosine (Scheme 2). Under the reported reaction conditions,[2i] condensation of aldehyde **2** with sarcosine (2 equiv) in toluene at reflux for 4 h, the expected tetrahydro-chromeno[4,3-*b*]pyrroles **7** was obtained in 70% yield. Increasing the reaction time to 16 h gave 1,2,4,9b-tetrahydrochromeno [4,3-*b*]pyrrole **7** in 73% yield together with the formation of the corresponding aromatized derivative **8** obtained in low yield (11%). Oxidation of compound **7**, using Pd/C in refluxing ethyl acetate for 24 h, afforded 1,4-dihydrochromeno[4,3-*b*]pyrrole **8** in 75% yield.



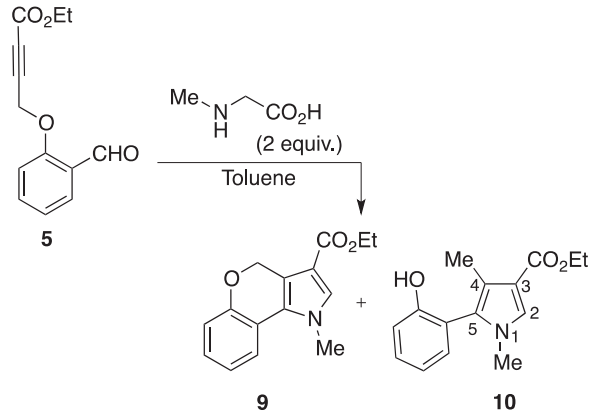
Scheme 1. Synthesis of *O*-propargylic, *O*-allenyl and *O*-buta-2,3-dienyl salicylaldehyde derivatives.



Scheme 2. Synthesis of tetrahydrochromeno[4,3-*b*]pyrrole **7** and dihydrochromeno [4,3-*b*]pyrrole **8** from *O*-propargylsalicylaldehyde (**2**) and sarcosine.

We extended the study to the reactivity of sarcosine towards salicylaldehyde **5**, bearing an activated alkyne (Table 1). Carrying out the reaction in refluxing toluene for 1 h, the corresponding 1,2,4,9b-tetrahydrochromeno[4,3-*b*]pyrrole was not formed and instead pyrrole **10** was isolated in 16% yield (entry 1). The structural assignment of this compound was based on one-dimensional ^{1}H and ^{13}C NMR spectra and confirmed by two-dimensional HMQC spectrum. The ^{1}H NMR spectrum showed a signal with a chemical shift of 2.14 ppm corresponding to methyl protons. In the HMQC spectrum, a proton having a chemical shift of 7.40 ppm showed connectivity with the carbon with the chemical shift 128.9 ppm, which was assigned to carbon C-2. On the other hand, no connectivity was observed for a proton with the chemical shift of 5.32 ppm confirming that it belongs to the hydroxyl group.

Table 1
Synthesis of chromeno[4,3-*b*]pyrrole **9** and pyrrole **10** from salicylaldehyde **5** and sarcosine



Entry	Reaction conditions	Isolated yield **9** (%)	Isolated yield **10** (%)
1	Reflux, 1 h[a]	—	16
2	Reflux, 2 h[a]	<5[b]	75
3	Reflux, 4 h[a]	<1[b]	81
4	Reflux, 15.5 h[a]	<3[b]	81
5	95 °C, 4 h[c]	<3[b]	15
6	MW, 120 °C, 5 min	—	—
7	MW, 150 °C, 15 min	<3[b]	52

[a] Dean–Stark apparatus was used.
[b] Compound **9** could not be isolated in pure form.
[c] Molecular sieves (4 Å).