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Synthesis of benzopyranopyrrolidines via 1,3-dipolar cycloaddition of nonstabilized azomethine ylides with 3-substituted coumarins

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ABSTRACT

A three-component reaction of 3-substituted coumarins with *N*-alkyl-α-amino acids and aldehydes gave 1-benzopyrano[3,4-*c*]pyrrolidines as a result of a 1,3-dipolar cycloaddition of an intermediate non-stabilized azomethine ylide at the double bond of the coumarin system in moderate to good yields. In most cases, high regio- and stereo-selectivity of the [3+2] cycloaddition was observed.

1. Introduction

A decarboxylative reaction of *N*-alkyl-α-amino acids with carbonyl compounds is one of the most convenient methods to generate nonstabilized azomethine ylides for [3+2] cycloaddition with electron-deficient alkenes.[1] As this method has been developed relatively recently, by Grigg and Tsuge in the late 1980s, the chemistry of nonstabilized azomethine ylides obtained in these reactions is studied significantly less in comparison with other 1,3-dipoles.[2] Their reactions with 3-substituted coumarins are interesting, first, to study the regio- and stereo-selectivity of the cycloaddition with asymmetric trisubstituted alkenes; second, in view of the biological activity of adducts.

It has been found that *R*,*R*-benzopyranopyrrolidine **1** is an α_1 adrenoreceptor antagonist, whereas *R*,*R*-benzopyranopyrrolidine **2** is an antagonist of 5-HT_{2C} receptors with respect to 5-HT_{2A}.[3] Benzopyranopyrrolidine **1** named Fiduxosin shows an α_{1a}/α_{1b} selectivity for adrenoreceptors; it was suggested as a promising pharmaceutical agent for the treatment of benign prostatic hyperplasia.[3f] Very recently, the synthesis of isomeric 2-benzopyranopyrrolidine **3**, which was found to be serotonin 5-HT_{2C} receptor agonist has been reported[3g] (Fig. 1).

The key stage in the synthesis of compounds **1** and **2** consists of a cycloaddition of nonstabilized azomethine ylides onto benzopyranones; however, information about such reactions in the coumarin series was quite limited.[2e,f,3g] In a preliminary communication,[4] we described the synthesis of 1-benzopyrano[3,4-*c*]pyrrolidines from 3-substituted coumarins and a symmetric azomethine ylide derived from sarcosine and formaldehyde. [3+2] cycloaddition of these coumarins with asymmetric ylides generated from proline and

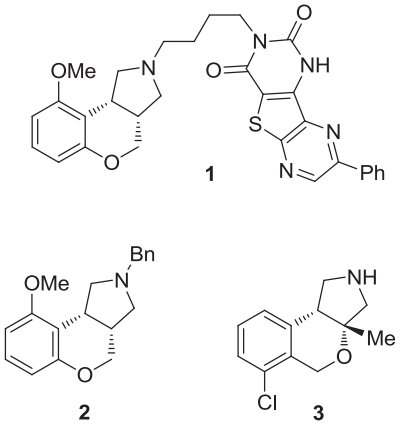

Fig. 1. Benzopyranopyrrolidine drugs candidates.

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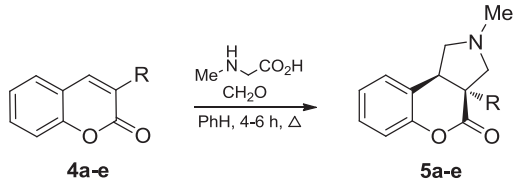
formaldehyde or benzaldehyde gave one diastereomer after crystallization of salts and indicated a good selectivity of the reaction. Given the broad utility of benzopyranopyrrolidines in medicinal chemistry and continuing our research in this field,[5,6] we have extended this to a number of coumarins and azomethine ylides, as well as isolating some minor diastereomers and establishing their structures. In addition, the study of the chemical properties of the adducts has begun.

2. Results and discussion

2.1. 1,3-Dipolar cycloaddition of nonstabilized azomethine ylides with 3-substituted coumarins

We have found that refluxing of sarcosine, paraformaldehyde and coumarins **4a**–**e** in benzene for 4–6 h with azeotropic removal of water results in benzopyranopyrrolidine derivatives **5a**–**e** (yields 76–92%) (Scheme 1). Treatment of products **5a**,**c** with oxalic acid provided conversion of these liquid pyrrolidines into analytically pure crystalline oxalates without chromatographic purification. Adducts **5b**,**d**,**e** were purified by flash chromatography using silica gel. On the other hand, 3-methylcoumarin reacts very sluggishly with this ylide, and after refluxing for 7 h only 27% of the desired product was observed in the crude reaction mixture according to the ^{1}H NMR spectroscopic data.



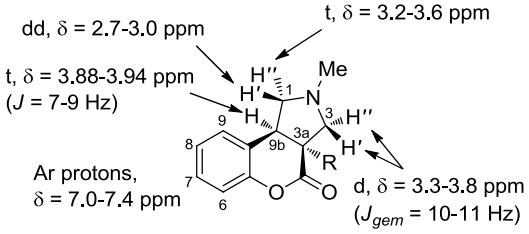
4a-e **5a-e**

Comp. **4**, **5**	R	Yield (%)	Product's form	Mp (°C)
a	H	78	oxalate	191–193
b	CN	76	free base	liq.
c	CO_2Et	84	oxalate	164–166
d	$CONMe_2$	87	free base	96–98
e	$PO(OEt)_2$	92	free base	126–128

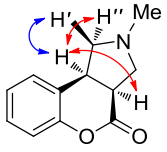
Scheme 1. Synthesis of 2-methyl-4-oxo-1,2,3,3a,4,9b-hexahydrochromeno[3,4-*c*]pyrroles **5a**–**e**.

The structures of products **5a**–**e** were determined by elemental analyses, HRMS and their ^{1}H and ^{13}C NMR spectra as well as 2D ^{1}H–^{13}C HMQC, HMBC, and ^{1}H–^{1}H NOESY experiments. The ^{1}H NMR spectra of oxalates **5a**,**c**,**d** in DMSO-d_6 contain the characteristic signals: a doublet of doublets for the H-1′ proton at δ 2.7–3.0 ppm, which is subject to the shielding effect of the benzene moiety in the *cis*-position; a triplet for H-1″ at δ 3.2–3.6 ppm (this proton manifests itself at δ 3.20–3.27 ppm in the presence of an ethoxycarbonyl or dimethylamide group at the 1,3-*cis*-position that show a shielding effect[7]); two doublet of doublets or two doublets for the H-3′ and H-3″ geminal protons at δ 3.3–3.8 ppm (J_{gem}=10–11 Hz); a quartet or a triplet for the H-9b benzyl proton at δ 3.88–3.94 ppm (J=7–9 Hz). The signals for the H-6 and H-8 aromatic protons are observed at δ 7.03–7.06 and 7.14–7.17 ppm, respectively, whereas the partially overlapping signals for H-7 and H-9 appeared at δ 7.25–7.35 ppm. It is well known that synchronism of the reactions of nonstabilized azomethine ylides with alkenes results in a *cis*-fusion in the new pyrrolidine ring.[1–3] This was confirmed in the ^{1}H–^{1}H NOESY experiment of the oxalate **5a** by considering the cross-peaks intensities of proton H-9b with H-1′, H-1″, and H-3a (Fig. 2).

*^{1}H NMR (400 MHz, DMSO-d_6) data of the oxalates **5a,c,d***



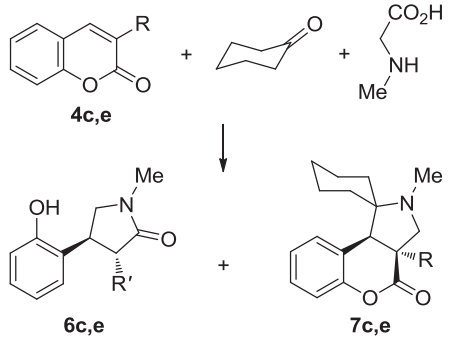
*^{1}H-^{1}H NOESY cross-peaks of the oxalate **5a***



red - strong NOE interactions
blue - weak NOE

Fig. 2. Diagnostic ^{1}H NMR signals and NOE correlations of benzopyranopyrrolidine oxalate **5a**.

Reaction of 3-substituted coumarins with the asymmetrical nonstabilized azomethine ylide generated in situ by the condensation of sarcosine and cyclohexanone led to unexpected results (Scheme 2). This ylide reacted with coumarins **4c**,**e** to give 4-aryl-2-pyrrolidones **6c**,**e** as the major products in 30% and 47% yields, respectively. A possible mechanism for their formation has been described previously.[5] For this reason, the yields of adducts **7c**,**e** resulting from the classical 1,3-dipolar cycloaddition were considerably reduced (17% and 20%, respectively). Compounds **7c**,**e** were isolated from a crude reaction mixture by simple acidification with dilute HCl (5 equiv) followed by separation of the aqueous layer, neutralization with $NaHCO_3$, and subsequent flash chromatography over silica gel (Scheme 2).



R = CO_2Et (**c**), $PO(OEt)_2$ (**e**)
R′ = $CONMe_2$ (**c**), $PO(OEt)_2$ (**e**)

Scheme 2. Reaction with asymmetrical azomethine ylides from sarcosine and cyclohexanone.

We have also examined the cycloaddition behaviour of proline and formaldehyde using coumarins **4** as the trapping dipolarophiles and found that fused pyrrolizidines **8** are produced as the major products (Scheme 3). The reactions of coumarins **4a**,**b** with proline and formaldehyde resulted in the formation of complex and difficult to separate mixtures of isomers and their hydrolysis products. In contrast, coumarins **4c**–**g** gave much more stable adducts. According to the ^{1}H NMR data, the crude reaction mixture of the cycloaddition with 3-ethoxycarbonylcoumarin (**4c**) consisted of four diastereomers with the stereochemistry as shown (Scheme 3).