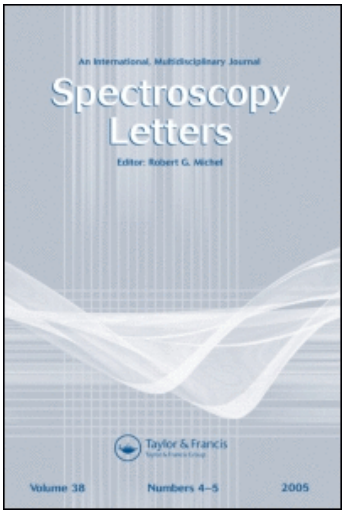

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Azetidin-2-one Versus Chroman-2-one: Application of ^{1}H-^{13}C COSY NMR and Mass Spectroscopy in Structure Elucidation–Class of Compounds

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ABSTRACT Azetidin-2-ones, commonly known as β-lactams, constitute a biologically important class of compound. Treatment of azetidin-2-ones with alkali is known to form diverse types of compounds depending on the stability of the ring. In many cases, the ring is retained in the product at the cost of transformation of substituents. Spectroscopy is the most important tool to characterize the organic compounds. However, in some cases the structures of the products are so closely related that simple IR, ^{1}H NMR, and ^{13}C NMR spectra do not lead to unambiguous structure elucidation. This article reports a novel application of ^{1}H-^{13}C COSY NMR and mass spectroscopy in determining unequivocally an azetidin-2-one ring structure instead of a chroman-2-one ring structure for the product obtained by treatment of 1-benzhydryl-3,3-bis(4-methylphenyl)-4-[2-(*o*-di*p*-tolylacyl)hydroxyphenyl]-2-azetidinone with ethanolic sodium hydroxide at room temperature.

KEYWORDS azetidin-2-one, chroman-2-one, ^{1}H-^{13}C COSY NMR, mass spectroscopy

INTRODUCTION

Spectroscopy is the most important experimental technique to determine the structures of organic compounds including azetidin-2-ones. A strong absorption band around 1750 cm^{-1} in the IR spectra characterizes the azetidin-2-ones.[1] Treatment of azetidin-2-ones with alkali is known to form diverse types of compounds depending on the stability of the ring[1–4] (Scheme 1). In many cases, the ring is retained in the product at the cost of transformation of substituents.[1,5] Often, the structures of the products might be so closely related that IR spectroscopy and one-dimensional NMR spectroscopy may not lead to a convincing conclusion. For example, the structures of chroman-2-one and azetidin-2-one (Fig. 1) are too close to distinguish between them on the basis of IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. The molecular formulas and so the masses of both products are the same. However, a different mass fragmentation pattern

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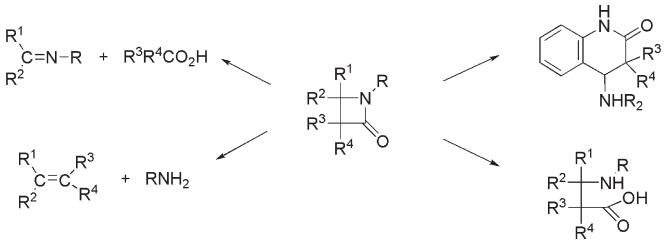


SCHEME 1 Cleavage of Azetidin-2-one Ring.

can be anticipated. The current article reports a novel application of ^{1}H-^{13}C COSY (Correlation Spectroscopy) NMR and mass spectroscopy in determining unequivocally an azetidin-2-one ring structure instead of a chroman-2-one ring structure for the product obtained by treatment of 1-benzhydryl-3,3-bis(4-methylphenyl)-4-[2-(*o*-di*p*-tolylacyl)hydroxyphenyl]azetidin-2-one with ethanolic sodium hydroxide at room temperature.

MATERIALS AND METHODS

The IR spectrum was recorded on a PerkinElmer 781, Shimadzu, RSA IR spectrophotometer (Bruker, Germany) using KBr disk of the sample. The ^{1}H NMR and ^{13}C NMR spectra were recorded in a $CDCl_3$ solution at 300 MHz and 75.4 MHz, respectively, on a Bruker 300 MHz spectrometer. The mass spectra were recorded on a Finnigan LC Q^{DECA} mass spectrometer (Finnigan, USA).

The substrate azetidin-2-one **1** was synthesized by the 2.2:1 molar reaction of the bis(4-methylphenyl)ketene with *N*-salicylidenediphenylmethanamine according to the reported method.[6]

Reaction of Azetidin-2-one 1 with Sodium Hydroxide

An equimolar solution of the azetidin-2-one (0.05 g) **1** and sodium hydroxide in 10 ml ethanol was stirred at room temperature for 30 min. The solution was neutralized with hydrochloric acid and extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The crystallization of the residue with ethanol afforded the white crystalline product in quantitative yield. The spectral data of the product is described below.

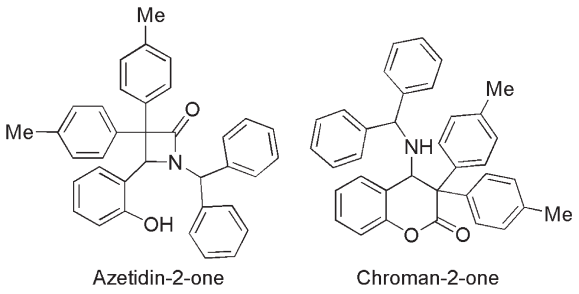


FIGURE 1 Structures of Closely Related Azetidin-2-one and Chroman-2-one.

M.p. 257°C; IR (KBr, cm^{-1}): 3360, 1725; ^{1}H NMR ($CDCl_3$, δ ppm): 7.64 (dd, 2H, arom, $J = 1.0$, 7.8 Hz), 7.35–7.27 (m, 6H, arom), 7.20 (m, 4H, arom), 7.11 (d, 2H, arom, $J = 7.8$ Hz), 7.07 (d, 2H, arom, $J = 8.4$ Hz), 6.93 (t, 1H, arom, $J = 7.2$ Hz), 6.78 (d, 2H, arom, $J = 7.8$ Hz), 6.76 (d, 1H, arom, $J = 7.8$ Hz), 6.60 (d, 1H, arom, $J = 7.8$ Hz), 6.50 (d, 1H, arom, $J = 7.8$ Hz), 5.90 (s, 1H, ring CH), 5.80 (s, 1H, OH, D_2O exchangeable), 5.61 (s, 1H, N-CH), 2.34 and 2.13 (two s, 6H, Me); ^{13}C NMR ($CDCl_3$, δ ppm): 171.0 (*C*=O), 154.0 (*C*-OH), 139.0, 138.7, 138.5, 136.4, 136.0, 135.8, 129.2, 129.0, 128.8, 128.5, 128.48, 128.46, 128.4, 128.2, 127.7, 127.6, 127.5, 127.47, 122.3, 120.0, 114.9 (22 arom C), 71.8 [*C*-(4-$MeC_6H_4)_2$], 62.7 (N-CH), 61.1 (C-4), 21.1, 21.0; MS (*m*/*z*): 509 (M^+), 300 (M^+-Ph_2CHNCO), 285, 222 (di*p*-tolylketene), 165, 91; found: C, 84.38%; H, 6.55%; N, 2.96%; $C_{36}H_{31}NO_2$ req.: C, 84.84%; H, 6.13%; N, 2.75%.

RESULTS AND DISCUSSION

Treatment of the azetidin-2-one **1** with sodium hydroxide in ethanol at room temperature afforded a white crystalline product. The IR spectrum of the product showed absorption bands at 1725 and 3360 cm^{-1} indicating the presence of a carbonyl group and a secondary amino or hydroxyl group in it. The ^{1}H NMR spectrum of the compound showed eight aromatic protons and six methyl protons less than the substrate. Furthermore, there were only two methine proton singlet signals (δ 5.9 and 5.61 ppm) instead of three in the substrate. A D_2O exchangeable proton was also observed in the product. The analysis of ^{1}H NMR data indicated the loss of bis(4-methylphenyl)acyl group from the substrate. This result was further substantiated by ^{13}C NMR spectral study. The ^{13}C NMR spectrum showed 22 aromatic carbons (δ 154.0–114.9 ppm), only one carbonyl carbon at δ 171 ppm, and two methine carbons at 62.7 and 61.1 ppm in the compound. These IR and NMR data are in agreement with azetidin-2-one structure for the

product that can be obtained by selective ester cleavage in the substrate. However, these data are also very close to the attempted product chroman-2-one (Fig. 1) that can be obtained by intramolecular attack of phenolate, generated under alkaline condition, on the carbonyl group of the substrate's azetidin-2-one ring. It was therefore considered pertinent to study the mass fragmentation pattern and HMQC (Heteronuclear Multiple Quantum, Coherence) and HMBC (Heteronuclear Multiple Bone Connectivity) in ^{1}H-^{13}C COSY NMR spectra. These studies led to azetidin-2-one structure **2** for the product. The significant correlations are discussed in the succeeding paragraph.

The HMQC showed the correlation of protons at δ 5.90 and 5.61 ppm with carbon signals at δ 61.1 and 62.7 ppm, respectively. The D_2O exchangeable proton at δ 5.8 ppm did not show HMQC correlation with any carbon signal. This proton, however, showed HMBC correlation with carbon signal at δ 154.0 ppm due to aromatic carbon attached to oxygen atom (Fig. 2). This correlation was a vital clue in favor of azetidin-2-one structure **2**. If the chroman-2-one structure is considered, the D_2O exchangeable proton would be N-H, that is, farther by four atoms from oxygen-bearing aromatic carbon, and is not expected

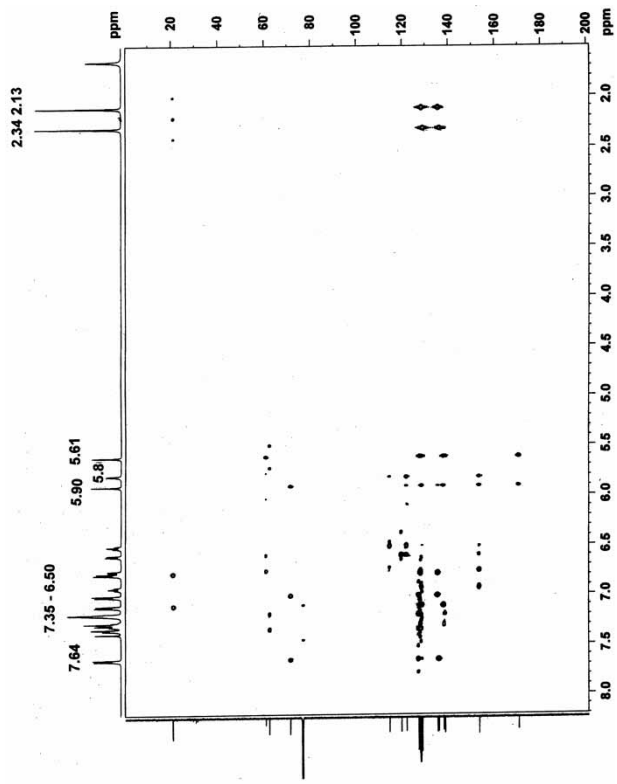
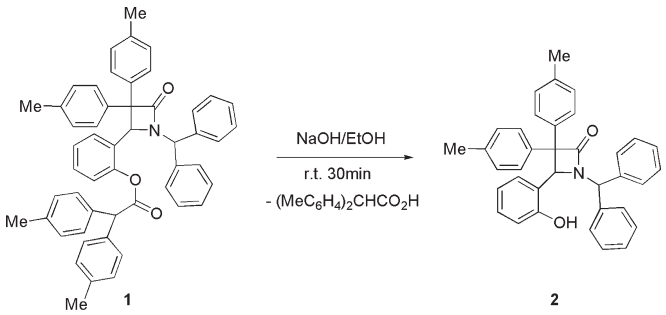


FIGURE 2 ^{1}H-^{13}C COSY NMR (HMBC) Spectra of 2.



SCHEME 2 Reaction of Azetidin-2-one with Ethanolic Sodium Hydroxide.

to show correlation with it. Furthermore, the D_2O exchangeable proton did not show any correlation with two methine carbon signals excluding the chroman-2-one structure. The singlet proton signal at δ 5.90 showed HMBC correlations with carbon signals at δ 61.1, 71.8 (C-3), 154.0 and 171.0 (C═O). Accordingly, this proton signal has been assigned to azetidin-2-one ring methine proton (C-4), and the carbon signal at δ 61.1 ppm has been assigned to C-4 ring carbon. The singlet proton signal at δ 5.61 showed HMBC correlations with carbon signals at δ 61.1, 62.7, 171.0 but not with carbon signals at δ 71.1 and 154.0 ppm. Thus, the proton signal at δ 5.61 has been assigned to *N*–C*H*Ph_2 proton and the carbon signal at δ 62.7 has been assigned to the *N*-benzhydryl carbon.

The mass spectrum of the product showed the molecular ion peak at 509. The mass spectrum showed the ketene (222) and imine (287) as main fragments. It also showed considerable abundance of a mass fragment at 300. Although the fragment at 222 is possible from both azetidin-2-one and chroman-2-one structures, the fragment at 300 due to $C_6H_4(OH)CH{=}C(C_6H_4.Me)_2$ is possible only from the azetidin-2-one structure. The fragmentation of azetidin-2-one to the corresponding alkene and isocyanate is reported in the literature.[2]

The formation of the product can be easily explained by chemoselective hydrolysis of the ester by alkali (Scheme 2). Also at room temperature, the formation of azetidin-2-one by selective ester cleavage appears more logical in comparison with intramolecular attack of phenolate on azetidin-2-one ring carbonyl. However, the reaction at reflux temperature also led to exclusive formation of product **2**.

CONCLUSIONS

This article reports a significant application of 2D NMR and simple mass spectroscopic technique

in characterization of the new azetidin-2-one that has many structural parameters similar to chroman-2-one.

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