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Note

Formation and antimicrobial activity of 2-azetidinones from selective ester cleavage in 1,3,3-trisubstituted 4-[2′-(*O*-diarylacyl)hydroxyphenyl]-2-azetidinones

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Treatment of the 1,3,3-trisubstituted 4-[2′-(*O*-diarylacyl)-hydroxyphenyl]-2-azetidinones with sodium hydroxide in ethanol at room temperature lead to selective cleavage of the ester linkage in the substrates forming new 1,3,3-trisubstituted 4-(2′-hydroxyphenyl)-2-azetidinones, which have been characterized on the basis of analytical and spectral (IR, ^{1}H and ^{13}C NMR, MS) data. The structure elucidation also involves application of the HMQC and HMBC studies using 2-D NMR (^{1}H-^{13}C COSY) spectra. The antibacterial and antifungal activities of the products are reported.

Keywords: Azetidinones, antimicrobial activity, HMQC study, HMBC study

Recent years have witnessed extensive investigation on application of the 2-azetidinones in synthesis of the diverse types of biologically important compounds including β-amino acids and complex heterocyclic compounds[1,2]. The chemistry of substituents present at the 2-azetidinone ring nitrogen and carbons has been explored to synthesize heterocyclic compounds including new 2-azetidinones[3,4]. Some examples of the latter case include hydrogenation of alkene moiety present at C-4, and *N*-sulfonylation in *N*-unsubstituted 2-azetidinones for transformation of one 2-azetidinone into other[5,6]. The presence of pyrrol-2-yl group at C-4 position of the 1,3,3-triaryl-2-azetidinones led to cleavage of the 2-azetidinone ring forming either the corresponding imine and ketene derived product or the alkene and isocyanate derived product depending upon the reaction conditions[7,8]. The presence of *o*-aminophenyl group at C-4 position of the 2-azetidinones, however, led to the formation of the isoquinoline derivatives by intramolecular nucleophilic attack of the amino group on the azetidinone carbonyl group[9]. The present paper reports the reaction of the 2-azetidinones having *o*-(*O*-diarylacyl)hydroxyphenyl group on C-4 with sodium hydroxide in ethanol resulting in formation of new 2-azetidinones by selective cleavage of the ester moiety in substrates. The antibacterial and antifungal screening of the compounds have shown moderate to good activity.

Treatment of the 2-azetidinones **1** with sodium hydroxide in ethanol at room temperature for half an hour and usual work-up resulted in formation of a white crystalline product. The elemental analysis and spectroscopic studies such as IR, ^{1}H NMR and ^{13}C NMR indicated the products' structure as either 1,3,3-trisubstituted 2-azetidinones **2** or chroman-2-ones **3**. The application of ^{1}H-^{13}C COSY NMR (HMQC and HMBC) and mass spectroscopy established the 2-azetidinone structures **2** for the products.

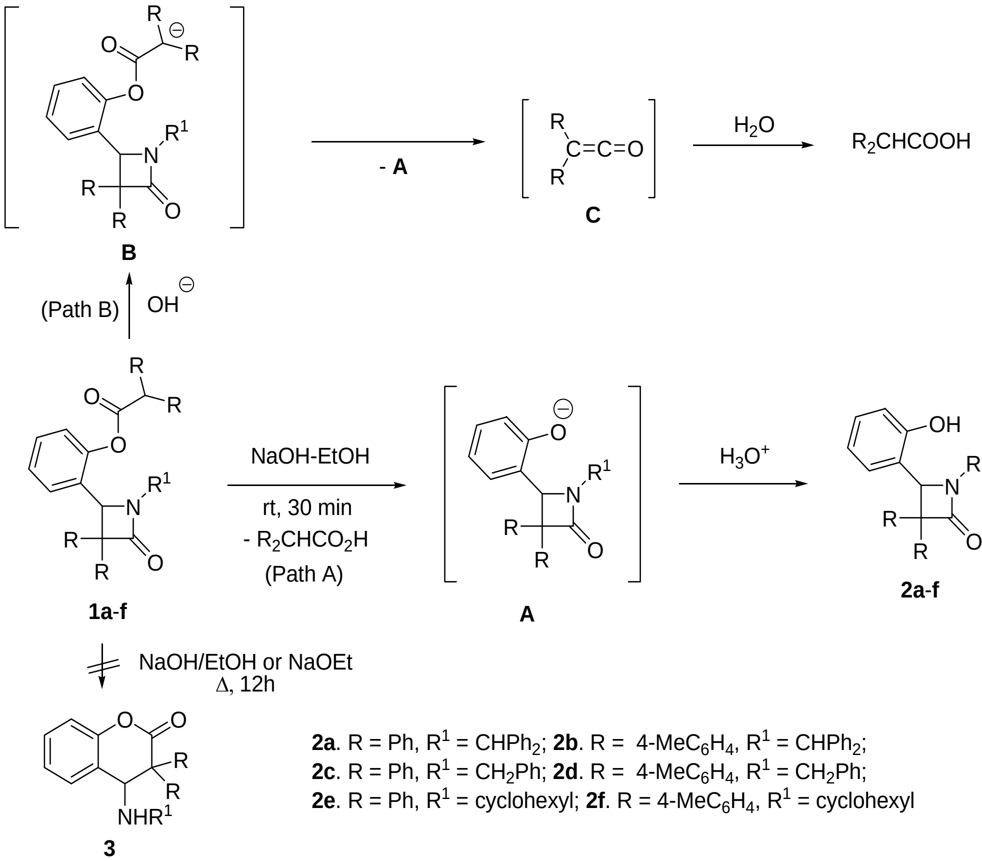
The IR spectra showed strong absorption band around 1720-40 cm^{-1}. The ^{1}H NMR spectra showed either eight or ten protons less in the aromatic region than the corresponding substrates indicating the removal of two 4-methylphenyl or phenyl rings. Furthermore the ^{1}H NMR spectra showed the loss of one singlet signal corresponding to a methine proton in the substrates. The ^{1}H NMR spectra also showed one singlet of one proton, which was D_2O exchangeable indicating the presence of either OH or NH group in the products. The ^{13}C NMR spectra showed the presence of only one low field signal around δ 170 ppm as against two in the substrates. The disappearance of either eight or ten aromatic protons and one methine proton in the ^{1}H NMR spectra of the products, and one carbonyl carbon together with a methine carbon in the ^{13}C NMR spectra clearly indicated the removal of diarylacyl groups from the substrates. The removal of latter groups, however, may lead to product with structure either **2** or **3**, and the spectral data discussed so far were almost in agreement with both the structures. The ^{1}H-^{13}C COSY spectra (HMQC) showed that the D_2O exchangeable proton was not correlated to any carbon again confirming its attachment either to oxygen or nitrogen. The ^{1}H-^{13}C COSY spectra (HMBC), however, showed that this signal was correlated to carbon signal at δ 154-155 ppm, which was considered due to aromatic carbon attached to oxygen. This correlation is justified for structure **2**, but not for **3** because in the latter case the aromatic carbon bearing the oxygen is separated from NH proton by four bonds. The mass spectra of the products showed fragments at 272 in **2a,c,e** and at 300 in **2b,d,f**. These fragments were due to alkenes Ph(OH)CH=CPh$_2$ or Ph(OH)CH=C(C$_6$H$_4$Me)$_2$, and were not feasible from structure **3**. A detailed study on structural elucidation of **2b** is recently reported[10].

Treatment of the substrates **1** either with sodium hydroxide or sodium ethoxide at reflux temperature failed to open the 2-azetidinone ring and afforded the products **2** identified on the basis of comparison with the compounds obtained by treatment of **1** with sodium hydroxide at room temperature.

The formation of products **2** can be explained by selective cleavage of the ester linkage in the product, which may occur in two different fashions. First, the hydroxide ion may attack on ester carbonyl group to form diarylacetic acids and 2-azetidinones with phenoxide group on C-4 (Path A), which can be protonated to afford the products (**Scheme I**). Secondly, the base may abstract a methine proton from diarylacyl groups (Path B) leading to the carbanion stabilized by the carbon-oxygen double bond. The cleavage of O-CO bond in this case would lead to the formation of diarylketenes besides the 2-azetidinones with phenoxide on C-4. The former compound would react with water eventually producing diarylacetic acids. The steric factor due to the presence of two phenyl ring on C-3 of the 2-azetidinone ring appears to be responsible for no reaction of either hydroxide or phenoxide ion with amide carbonyl group.

It is noteworthy to mention that the 2-azetidinones **2** cannot be synthesized by the [2+2]-cycloaadition of the diarylketenes with the corresponding *N*-salicylideneamines because the reaction of diarylketenes occurs mainly at phenolic hydroxyl group of the imines[11]. Thus, the reaction of 2-azetidinones **1** with sodium hydroxide offers an easy method for synthesizing **2**.

All the compounds screened showed better activity against bacteria and fungus C. *mycoderma* than the corresponding parent 2-azetidinone **1**. The MICs were observed in the range of 0.5-10 μg/mL. The 2-



2a. R = Ph, R^1 = CHPh$_2$; **2b**. R = 4-MeC$_6$H$_4$, R^1 = CHPh$_2$;
2c. R = Ph, R^1 = CH$_2$Ph; **2d**. R = 4-MeC$_6$H$_4$, R^1 = CH$_2$Ph;
2e. R = Ph, R^1 = cyclohexyl; **2f**. R = 4-MeC$_6$H$_4$, R^1 = cyclohexyl

Scheme I

azetidinone **2d**, bearing a benzyl group on ring nitrogen and two 4-MeC_6H_4 groups on C-3, was observed as the most active compound in the series with MIC of 0.5 μg/mL against E. *coli*, B. *subtilis* and S. *aureus*. The activity on C. *mycoderma* was independent of the substituents either on C-3 or on ring nitrogen as all the compounds inhibited the growth of this species at MIC of 5 μg/mL.

Experimental Section

Melting points were recorded on a Stuart Scientific melting point apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer-781 IR spectrophotometer using KBr disc of the sample. The ^{1}H and ^{13}C NMR spectra were recorded in a $CDCl_3$ solution at 300 MHz and 75.4 MHz, respectively, on a Bruker^{TM} 300 MHz spectrometer. The mass spectra were recorded on Finnignan LC Q^{DECA} mass spectrometer. The antimicrobial screening was done according to the reported method[11].

The 2-azetidinones **1a-f** were synthesized by the 2.2:1 molar reaction of the 2-diazo-1,2-diarylethanones with *N*-salicylideneamines according to the reported method[13]. The compounds **1e** and **1f** are new. Their characterization data is described below.

1-Cyclohexyl-3,3-diphenyl-4-[2′-(*O*-diphenylacyl)-hydroxyphenyl]-2-azetidinone 1e. Yield 87%, m.p. 132-33°C; IR (KBr): 1761, 1742 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.48-7.26 (m, 18H, arom), 7.17 (m, 1H, arom), 7.10 (dd, 3H, arom), 6.85 (dd, 2H, arom), 5.37 and 5.36 (two s, 2H, CH), 3.42 (tt, 1H, CH), 1.85-1.41 (m, 6H, CH_2), 1.26-1.05 (m, 4H, CH_2); ^{13}C NMR ($CDCl_3$): δ 170.9, 169.7, 149.2, 141.1, 137.9, 137.7, 129.4, 129.0, 128.9, 128.8, 128.7, 128.6, 128.6, 128.5, 128.4, 128.3, 127.9, 127.8, 127.6, 127.1, 127.0, 126.6, 125.3, 121.9, 72.0, 57.1, 52.9, 31.2, 30.5, 25.2, 25.1, 25.0; MS (*m/z*): 591 (M^+), 466 (M^+-Chex-N-C=O), 397 (M^+-Ph_2C=C=O), 272 (Ph(OH)CH=CPh_2), 194 (Ph_2C=C=O), 167; Anal. Calcd for $C_{41}H_{37}NO_3$: C, 83.22; H, 6.30; N, 2.37%. Found: C, 82.92; H, 6.57; N, 2.15%.

1-Cyclohexyl-3,3-bis(4-methylphenyl)-4-[2′-(*O*-diphenylacyl)hydroxyphenyl]-2-azetidinone 1f. IR (Nujol): 1757, 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.33-6.80 (m, 20H, arom), 5.31 (s, 1H, CH), 5.26 (s, 1H, CH), 3.40 (tt, 1H, N-CH), 2.42, 2.39, 2.35, 2.21 (four s, 12H, Me), 1.79-1.35 (m, 6H, CH_2), 1.23-1.01 (m, 4H, CH_2).

Reaction of 2-azetidinones with sodium hydroxide

An equimolar solution of the 2-azetidinones (0.06 g) **1** and sodium hydroxide in 10 ml of 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 sulphate. The solvent was evaporated under reduced pressure. The fractional crystallization of the residue with ethanol afforded the crystalline 2-azetidinones in quantitative yields.

1-Diphenylmethyl-3,3-diphenyl-4-(2′-hydroxyphenyl)-2-azetidinone 2a. m.p. 276°C; IR (KBr): 3339, 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 9.07 (s, 1H, OH, D_2O exchangeable), 7.89 (dd, 2H, arom, *J* = 1.5, 8.7 Hz), 7.49 (m, 2H, arom), 7.47-7.15 (m, 12H, arom), 7.00-6.93 (m, 4H, arom), 6.82 (m, 3H, arom), 6.40 (m, 1H, arom), 6.00 (s, 1H, ring CH), 5.60 (s, 1H, N-CH); ^{13}C NMR ($CDCl_3$): δ 169.6 (*C*=O), 155.4 (*C*-OH), 141.9, 140.0, 139.6, 139.4, 128.7, 128.5, 128.3, 128.2, 128.1, 127.8, 127.6, 127.4, 127.3, 126.9, 126.3, 122.4, 118.9, 114.8, 72.0 (*C*-Ph_2), 63.0, 61.3; MS (*m/z*): 481 (M^+), 285, 272 (M^+-Ph_2CHNCO), 194 (Ph_2C=C=O), 165, 77 ; Anal. Calcd for $C_{34}H_{27}NO_2$: C, 84.80; H, 5.65; N, 2.91%. Found: C, 84.41; H, 5.96; N, 2.75%.

1-Diphenylmethyl-3,3-bis(4-methylphenyl)-4-(2′-hydroxyphenyl)-2-azetidinone 2b. m.p. 257°C; IR (KBr): 3360, 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 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 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, 61.1, 21.1, 21.0; MS (*m/z*): 509 (M^+), 300 (M^+-Ph_2CHNCO), 285, 222 (di*p*-tolylketene), 165, 91; Anal.Calcd for $C_{36}H_{31}NO_2$: C, 84.84; H, 6.13; N, 2.75%. Found: C, 84.38; H, 6.55; N, 2.96%.

1-Benzyl-3,3-diphenyl-4-(2′-hydroxyphenyl)-2-azetidinone 2c. m.p. 222°C; IR (KBr): 3294, 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.76 (m, 2H, arom), 731-6.94 (m, 14H, arom), 6.80 (dd, 1H, arom, *J* = 1.5, 7.5 Hz), 6.73, (dd, 1H, arom, *J* = 0.9, 8.1 Hz), 6.64 (t, 1H, arom, *J* = 7.5 Hz), 6.23 (s, 1H, ring CH), 5.75 (s, 1H, D_2O exchangeable), 5.02 and 4.01 (two d, 2H, CH_2, *J* = 15.0 Hz); ^{13}C NMR ($CDCl_3$, δ ppm): 170.7 (*C*=O), 154.1 (*C*-OH), 140.8, 138.4, 135.2, 128.8, 128.7, 128.5, 128.4, 128.2, 127.9, 127.8, 127.7, 126.5, 121.8, 120.2, 115.2, 73.4 (*C*-Ph_2), 60.2 (ring *C*H), 44.7 (*C*H_2); MS (*m/z*): 405 (M^+), 272 M^+-$PhCH_2NCO$, 194 ($Ph_2C{=}C{=}O$), 165, 77; Anal.Calcd for $C_{28}H_{23}NO_2$: C, 82.94; H, 5.72; N, 3.45%. Found: C, 82.73; H, 5.95; N, 3.33%.

1-Benzyl-3,3-bis(4-methylphenyl)-4-(2′-hydroxyphenyl)-2-azetidinone 2d. m.p. 194°C; IR (KBr): 3279, 1720 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.00 (s, 1H, D_2O exchangeable), 7.70 (dd, 2H, arom *J* = 1.5, 8.1 Hz), 7.27-7.05 (m, 11H arom), 6.98 (t, 1H, arom, *J* = 6.0 Hz), 6.87-6.81 (m, 4H, arom), 6.59 (d, 1H, arom, *J* = 7.7 Hz), 5.70 (s, 1H, ring CH), 4.97 and 4.01 (two d, 2H, CH_2, *J* = 15.3 Hz), 2.28 and 2.10 (two s, 6H, Me); ^{13}C NMR ($CDCl_3$): δ 169.7 (*C*=O), 155.4 (*C*-OH), 139.3, 136.5, 136.2, 136.16, 136.0, 128.8, 128.6, 128.5, 128.2, 128.1, 127.9, 127.7, 127.5, 122.2, 119.2, 114.9, 72.8 [*C*-(4-$MeC_6H_4)_2$], 60.1 (ring *C*H), 43.9 (*C*H_2), 20.1, 20.0; MS (*m/z*): 433 (M^+), 300 (M^+-$PhCH_2NCO$), 285, 222 (di*p*-tolylketene), 194, 179, 165, 91 (PhMe); Anal.Calcd for $C_{30}H_{27}NO_2$: C, 83.11; H, 6.28; N, 3.23%. Found: C, 82.76; H, 6.55; N, 2.95%.

1-Cyclohexyl-3,3-diphenyl-4-(2′-hydroxyphenyl)-2-azetidinone 2e. m.p. 149 °C, IR (KBr): 3360, 1717 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.05 (bs, 1H, OH, D_2O exchangeable), 7.78 (dd, 2H, arom), 7.25-7.05 (m, 5H, arom), 6.87-6.70 (m, 4H, arom), 6.67 (dd, 2H, arom), 6.45 (t, 1H, arom), 6.05 (s, 1H, CH), 3.40 (tt, 1H, N-CH), 1.96-1.63 (m, 6H, CH_2), 1.18-1.13 (m, 4H, CH_2); ^{13}C NMR ($CDCl_3$): δ 171.1 (*C*=O), 154.5 (*C*-OH), 141.3, 138.8, 128.7, 128.5, 128.0, 127.8, 127.5, 127.3, 127.0, 126.5, 122.9, 119.6, 115.2, 71.9, 59.3, 53.5, 31.4, 30.6, 25.3, 25.2, 25.1; MS (*m/z*): 397 (M^+), 272 (M^+-Chex-N-C=O), 203 (Ph(OH)CH=N-Chex), 194 ($Ph_2C{=}C{=}O$), 166; Anal.Calcd for $C_{27}H_{27}NO_2$: C, 81.58; H, 6.85; N, 3.52%. Found: C, 81.40; H, 7.19; N, 3.21.

1- Cyclohexyl-3, 3 - bis(4-methylphenyl) - 4-(2′-hydroxyphenyl)-2-azetidinone 2f. m.p. 137°C; IR (KBr): 3355, 1715 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.90 (bs, 1H, OH, D_2O exchangeable), 7.72 (dd, 2H, arom), 7.26-6.98 (m, 4H, arom), 6.87-6.70 (m, 3H, arom), 6.75 (dd, 2H, arom), 6.50 (t, 1H, arom), 5.91 (s, 1H, CH), 3.42 (tt, 1H, N-CH), 2.26 & 2.08 (two s, 6H, Me), 1.83-1.51 (m, 6H, CH_2), 1.32-1.18 (m, 4H, CH_2); ^{13}C NMR ($CDCl_3$): δ 171.1 (*C*=O), 154.8 (*C*-OH), 139.0, 137.4, 128.7, 128.6, 128.3, 128.2, 128.0, 127.9, 127.6, 123.3, 122.0, 118.7, 115.1, 71.4, 59.3, 53.4, 31.4, 30.6, 25.4, 25.3, 25.1, 21.0, 20.9; MS (*m/z*): 425 (M^+), 300 (M^+-Chex-N-C=O), 285, 222 (di*p*-tolylketene), 203 (Ph(OH)CH=N-Chex), 91; Anal.Calcd for $C_{29}H_{31}NO_2$: C, 81.85; H, 7.34; N, 3.29%. Found: C, 81.56; H, 7.75; N, 2.95.

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