Unanticipated Products from Reductive and Oxidative Cleavages of 1-Substituted 3,3-diphenyl-1′-methylspiro [azetidine-2,3′-indoline]-2′,4-diones

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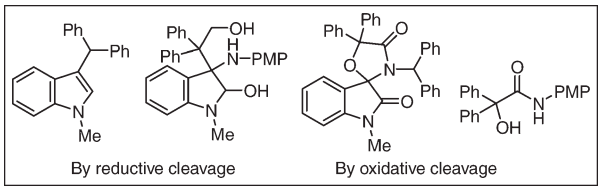

Titled spiroazetidinones **1a,b** undergo reductive cleavage on treatment with excess lithium aluminum hydride forming 3-benzhydryl-1-methylindole as the main product together with a γ-amino alcohol depending upon the substituent present on the azetidin-2-one ring. Treatment of 1a with Ce(IV) ammonium nitrate affords 2-hydroxy-*N*-(4-methoxyphenyl)-2,2-diphenylacetamide besides the anticipated *N*-unsubstituted 2-azetidinone, whereas a similar treatment of 1-benzhydryl-3,3-diphenyl-2-azetidinone 1b affords the ring expansion product 1,3-oxazolidin-4-one. The products have been characterized on the basis of satisfactory analytical and spectral (IR, ^{1}H and ^{13}C-NMR, DEPT, HMBC) data and their formation is discussed.

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INTRODUCTION

2-Azetidinone ring, commonly known as β-lactams, is the key structural feature in the famous class of antibiotics, β-lactam antibiotics [1]. Some β-lactams are also in clinical use as β-lactamase inhibitors and cholesterol absorption inhibitors [2–4]. The synthesis and biological screening of 2-azetidinones have been the principal focus of early researchers in the field. Recent years, however, have witnessed an extensive research in application of 2-azetidinones as synthons [5–10]. As a result, such compounds have found application in synthesis of diverse classes of compounds such as β-amino acid, γ-amino alcohols, aziridines, azetidines, pyrrole derivatives, and many other heterocyclic compounds of potential biological interest [5].

Recently, spiro-fused 2-azetidinones have drawn considerable interest because of some biological activities associated with such 2-azetidinone [11–24]. Efforts are on to explore their synthetic applications, which prompted us to study the synthesis, biological activity, and chemistry (reduction and oxidation) of 2-azetidinones spiro-fused to another biologically important structural motif, 2-indolinone. The product(s) of reduction of 2-azetidinones depends on the reducing agent used and the substituent present on the 2-azetidinone ring. For example, the reduction of *N*-Boc substituted 2-azetidinone with lithium aluminum hydride (LAH) results into formation of γ-amino alcohols quantitatively [25,26]. The N(1)-C(4) cleavage is reported in case of C(4)-formyloxy substituted 2-aztidinones using sodium borohydride [27]. Formation of azetidine is reported in some cases using LAH, monochloroalane, and Raney nickel [5,9]. However, 2-azetidinones having two phenyl rings on C-3 are mostly stable and have been observed inert to acids, bases, and some reducing agents as well [28]. There is an example of hydrolytic cleavage of 3,3-diphenylazetidin-2-one to an alkene and imine, but the cleavage is attributed to the presence of a 2-pyrrolyl group on C-4 position [29].

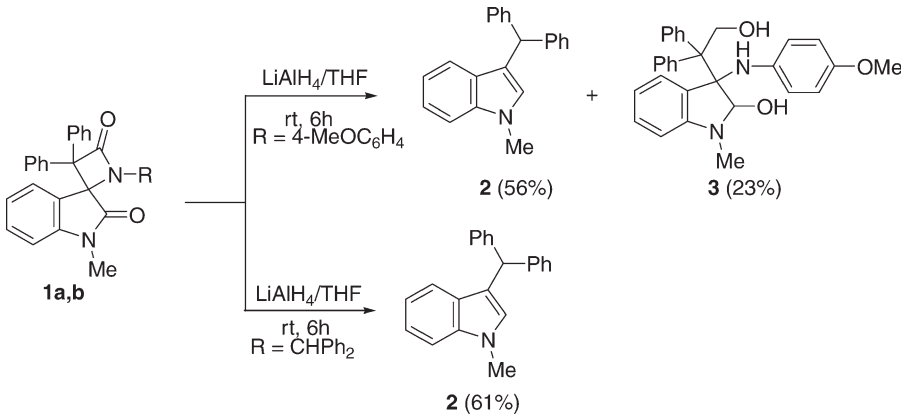
The *N*-dearylation (4-methoxyphenyl group) and *N*-dealkylation (*bis*-4-anisylmethyl group, 4-methoxyphenethyl group) of 2-azetidinones by oxidative cleavage on treatment with well known oxidizing agent Ce(IV) ammonium nitrate (CAN) are well-known reactions [30–34]. This reaction opens up room for a wide variety of transformation on the 2-azetidinone ring.

We wish to report in this article the results obtained from treatment of 1-(4-methoxyphenyl)- and 1-benzhydryl-3,3-diphenyl-1′-methylspiro[azetidine-2,3′-indoline]-2′,4-dione **1a,b** with LAH and with CAN leading to formation of products from reductive and oxidative cleavages, respectively. To the best of our knowledge, 2-azetidinones having two phenyl groups on C-3 position of the ring have not been subjected to such studies in the past.

RESULTS AND DISCUSSION

Reactions with LAH. Treatment of the 1-(4-methoxyphenyl)-3,3-diphenyl-1′-methylspiro[azetidine-2,3′-indoline]-2′,4-dione **1a** [20] with 6.0 molar equivalents of LAH led to the formation of 3-benzhydryl-1-

Scheme 1



methylindole **2** which was identified by comparison of its NMR spectral data with the one reported earlier, and a γ-amino alcohol, 3-(2-hydroxy-1,1-diphenylethyl)-3-(4-methoxyphenylamino)-1-methylindolin-2-ol **3** (Scheme 1). It is noteworthy to mention that the indoles are compounds of biological significance, and their transformation is an area of current interest [35,36]. The synthesis of **2** has been reported recently by the reaction of benzhydrol with 1-methylindole using indium trichloride as a catalysts in toluene at 80°C for 15 h [37]. The formation of γ-amino alcohols as a sole product by reductive cleavage of 2-azetidinones and their application in the synthesis of oxazinanes have been reported recently [38]. However, partial reduction of the indolinone ring in this case was surprising. Thus, the presence of methylene carbon (CH_2), two quaternary carbons (spiro-carbon and *C*-Ph_2), and methine carbon (C2′) (see experimental) was confirmed by DEPT NMR spectroscopy. The *N*-methyl proton showed correlation with methine carbon at δ98 ppm in the HMBC NMR spectra.

Treatment of the 1-(diphenylmethyl)-3,3-diphenyl-1′-methylspiro[azetidine-2,3′-indoline]-2′,4-dione **1b** [21] with LAH in a similar manner as described for **1a** showed three spots on the TLC. Purification using silica gel column and *n*-hexane-ethyl acetate as eluent afforded the 3-benzhydryl-1-methylindole **2** as the main product. The other two products present in trace amounts could not be characterized due to low yields.

The product **2** may be formed by aromatization of an alkene obtained from the reduction of γ-lactam carbonyl to CH_2 and reductive cleavage of azetidin-2-one. The formation of an alkene by reductive cleavage of the 2-azetidinone ring is reported earlier [39]. The product **3** results from partial reduction of the C=O group of the indolinone ring and cleavage of the N-C(2) bond of the 2-azetidinone. No cleavage of the 2-indolinone ring occurred on treatment with LAH. Although some 3-alkylimino-1-methylindolin-2-ones, similar to the ones used for the synthesis of 2-azetidinones, are reported to give aniline derivatives as a result of complete reduction of the azomethine linkage and cleavage of the indoline ring in the presence of sodium borohydride [40], none of the two 2-azetidinones under study was found reactive to either sodium borohydride or monochloroalane.

Reaction with cerium(IV) ammonium nitrate. Treatment of the spiro-fused 2-azetidinone **1a** with CAN according to the method described in the literature [30,31] afforded the compound **4**, formed from the cleavage of N1-C4 and C3-C4 bonds of the 2-azetidinone ring, in reasonable yield besides the anticipated spiro-fused 2-azetidinone having unsubstituted nitrogen **5** (Scheme 2). A similar treatment of the 2-azetidinone **1b** with CAN afforded an unanticipated solid product **6** in 53% yield. This product has been characterized as 3-benzhydryl-5,5-diphenyl-1′-methylspiro[oxazolidin-2,3′-indolin]-4,2′-dione **6** on the basis of analytical and spectral data discussed briefly in the succeeding paragraph. The 1,3-oxazolidin-4-ones constitute a biologically important class and have been synthesized in the recent past either by treatment of *O*-allylacetamides with TBSOTf or by cyclocondensation of imines with α-hydroxy acids [41,42]. To the best of our knowledge, no any other product is reported from the oxidative cleavage of 2-azetidinones in the presence of CAN except the *N*-deprotected 2-azetidinones and product derived from the leaving group.

The IR spectrum of this compound showed a slightly broad but strong absorption band at 1732 cm^{-1} instead of 1760 and 1728 cm^{-1} as observed in the substrate **1b** indicating the presence of more than one carbonyl group in the product **6** which was further confirmed as two carbonyl carbons by ^{13}C-NMR spectra. The ^{1}H-NMR spectrum showed the same number of protons as in the substrate, but the splitting pattern of the aromatic protons and the chemical shift of the only methine proton were different from that in the substrate. As shown in

Scheme 2

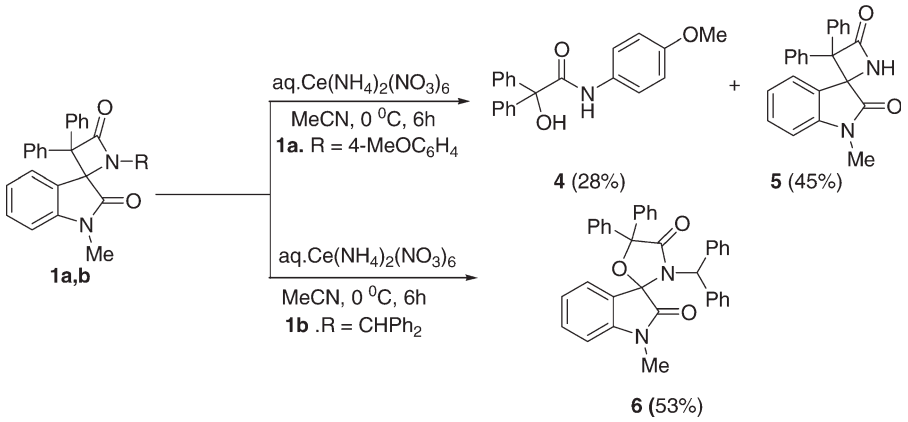


Figure 1, the methine proton at δ 5.88 ppm in the substrate **1b** shifted upfield to δ 5.61 ppm in product **6**. The ^{13}C-NMR spectrum showed two carbonyl carbons closer to each other (δ 171.5 and 170.5 ppm) than in the substrate (δ174.0, 169.5 ppm). Two quaternary carbons (established by DEPT) observed at δ 75.3 and 71.4 ppm in the ^{13}C-NMR spectrum of the substrate shifted downfield to δ 91.7 and 85.8 ppm indicating the presence of electronegative atom adjacent to them. The mass spectrum of the compound **6** showed the molecular ion peak at 536 that was 16 more than the mass of the substrate indicating addition of an oxygen atom or water molecule onto the substrate.

After establishing from the spectral data, elemental analysis, mixed mp with substrate **1b** and different R_f value on the TLC plate that the substance was different from the substrate, various possibilities with regard to structure were closely looked at. As we already had results from cleavage of N1-C4 and C3-C4 bonds in compound **1a**, we investigated the structures possible from cleavage of these bonds. The spectral data discussed above in combination with DEPT, HMQC, and HMBC of ^{1}H and ^{13}NMR signals suggested the compound as spiro-1,3-oxazolidin-4-one **6**. Because the methine proton signal at δ 5.60 ppm showed correlation with quaternary carbon signal at δ 91.7 and carbonyl carbon signal at δ170.5 ppm in the HMBC spectra, these two carbon signals have been assigned to spiro carbon (C2,3′) and carbonyl carbon of the oxazolidinone ring, respectively. The *N*-methyl proton correlated to the other low field carbon signal at δ 171.5, and hence, this later signal has been assigned to the indolinone ring carbonyl carbon.

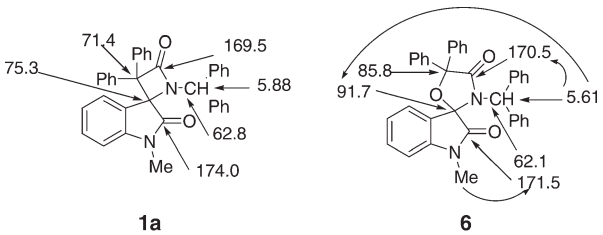


Figure 1. Significant ^{1}H- and ^{13}C-NMR signals and HMBC correlationship.

It seems from the formation of products **4** and **6** that after loss of electron from substrates to CAN water attaches itself on C-3 position of the 2-azetidinone ring and cleaves the ring besides *N*-dearylation. The cleavage of C3-C4 bond occurs in both the substrates, but the cleavage of N1-C4 bond depends upon the substituent present. In substrate **1a** having an *N*-C_6H_4-OMe-4 group, the cleavage of N1-C4 bond takes place affording the product **4**. In substrate **1b** having an *N*-$CHPh_2$ group, the N1-C4 bond does not cleave and the ring opened intermediate formed by cleavage of C3-C4 bond possibly undergoes oxidative cyclization to yield the ring expansion product 1,3-oxazolidin-4-one **6**.

CONCLUSIONS

In conclusion, the article reports hitherto unknown cleavage of spiro-fused 2-azetidionones ring and novel entry into 3-benzhydryl-1-methylindole and spiro-fused oxazolidine ring systems from spiro-fused 2-azetidinones.

EXPERIMENTAL

Melting points have been 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 Finnigan LC Q^{DECA} mass spectrometer.

The 2-azetidinones **1a,b** were synthesized by the reaction of 2-diazo-1,2-diphenylethanone with imines according to reported methods [20,21].

General procedure for the reaction of spiroazetidinones with LAH. LAH (0.05 g, 1.2 mmol) was added to a solution of an appropriate substrate **1** (0.2 mmol) in THF (4 mL). The mixture was stirred at room temperature until TLC showed complete disappearance of the substrate (6 h). The reaction mixture, after addition of a few drops of water, was filtered through celite. The filtrate was dried on anhydrous magnesium sulfate before removing the solvent on rotary evaporator. The residue was purified by thin layer chromatography on silica gel using *n*-hexane and ethyl acetate as eluent.

3-Benzhydryl-1-methylindole (2). Mp: 131–133°C (lit. 132°C); IR (KBr, cm^{-1}): 2927, 1600, 1469, 740; ^{1}H-NMR ($CDCl_3$, δ δ ppm): 7.22–6.86 (14H, arom.), 6.32 (s, 1H, C(2)-H), 5.58 (s, 1H, C-H), 3.61 (s, 3H, N-CH_3); ^{13}C-NMR ($CDCl_3$, δ ppm): 144.12, 137.45, 129.01, 128.73, 128.26, 127.38, 126.17, 121.62, 119.99, 118.82, 118.28, 109.11, 48.80, 32.68; Mass (*m*/*z*, r. i.): 298 (20), 297 (60), 296 (17), 220 (100), 167 (30). Anal. Calcd. for $C_{22}H_{19}N$: C, 88.85; H, 6.44; N, 4.71. Found: C, 88.63; H, 6.65; N, 4.70.

3-(2-Hydroxy-1,1-diphenylethyl)-4-(methoxyphenylamino)-1-methylindolin-2-ol (3). IR (KBr, cm^{-1}): 3325–3280, 2900, 1590; ^{1}H-NMR ($CDCl_3$, δ ppm): 7.38–7.16 (m, 12H, arom), 6.97 (t, 1H, arom), 6.49 (dd, 2H, arom), 6.32 (d, 1H, arom), 6.15 (dd, 2H, arom), 5.80 (bs, 1H), 5.70 (s, 1H, CH), 5.65 (bs, 1H), 4.09 (bs, 1H), 3.67 (s, 2H, CH_2), 3.57 (s, 3H, O**Me**), 2.94 (s, 3H, *N*-Me); ^{13}C-NMR ($CDCl_3$, δ ppm): 153.2, 151.7, 143.8, 140.1, 139.0, 129.7, 128.2, 127.9, 127.6, 127.0, 117.4, 117.0, 114.5, 104.9, 98.0 (C2′-H, DEPT), 78.6 (quaternary carbon, DEPT), 69.4 (CH_2, DEPT), 68.1 (quaternary carbon, DEPT), 55.6 (*O*-Me), 30.6 (*N*-Me); Mass (*m*/*z*, r. i.): 464 (M^+-2, 2), 446 (10), 428 (100), 296 (20), 268 (65), 252 (25), 237 (20), 223 (5), 196 (25), 167 (88), 146 (50), 122 (78), 77 (22). Anal. Calcd. for $C_{30}H_{30}N_2O_3$: C, 77.23; H, 6.48; N, 6.00. Found: C, 76.90; H, 6.70; N, 5.70.

General procedure for the reaction of spirozetidinones with cerium ammonium nitrate. A cold solution (0°C) of CAN (0.6 mmol) in 3 mL of distilled water was added drop wise to a solution of the appropriate 2-azetidinone (0.2 mmol) in acetonitrile (5.0 mL) maintained at 0°C. The reaction mixture was stirred at 0°C until TLC showed complete disappearance of the substrate (6 h). Distilled water (3 mL) was then added to the reaction mixture before extracting the mixture with ethyl acetate (10 mL × 2). The ethyl acetate extract was washed with saturated sodium hydrogen carbonate (5 mL). The aqueous layer was extracted again with ethyl acetate (5 mL). The combined organic extract was washed in turn with sodium hydrogen sulphite, sodium hydrogen carbonate, and sodium chloride. After drying over anhydrous magnesium sulphate and evaporation of ethyl acetate on a rotary evaporator, the residue was purified by column chromatography using *n*-hexane-ethyl acetate mixture. The characterization data of products are given below.

2-Hydroxy-N-(4-methoxyphenyl)-2,2-diphenylacetamide (4). IR (KBr, cm^{-1}): 3325, 2900, 1660; ^{1}H-NMR ($CDCl_3$, δ ppm): 8.34 (bs, 1H), 7.55–7.49 (m, 6H), 7.48–7.40 (m 6H), 6.88 (dd, 2H), 5.32 (s, 1H), 3.80 (s, 3H); ^{13}C-NMR ($CDCl_3$, δ ppm): 170.8, 156.7, 142.7, 130.3, 128.5, 128.4, 127.6, 121.5, 114.2, 81.9, 55.5; Mass (*m*/*z*, r. i.): 333 (M^+, 10), 310 (5), 183 (100), 123 (20), 105 (88), 77 (45). Anal. Calcd. for $C_{21}H_{19}NO_3$: C, 75.66; H, 5.74; N, 4.20. Found: C, 75.38; H, 6.00; N, 3.95.

3,3-Diphenyl-1′-methylspiro[azetidine-2,3′-indoline]-2′,4-dione (5). Mp: 198–200°C, IR (KBr, cm^{-1}): 3248, 1767, 1705, 1612, 1477, 1362; ^{1}H-NMR ($CDCl_3$, δ ppm): 7.50–6.72 (13H, arom.), 6.53 (s, 1H, N-H), 6.27 (dd, J = 7.5, 0.6 Hz, 1H, arom), 3.24 (s, 3H, *N*-CH_3), ^{13}C-NMR ($CDCl_3$, δ ppm): 175.48, 169.70, 143.76, 138.51, 138.08, 130.36, 128.31, 128.29, 127.98, 127.60, 127.38, 126.53, 126.39, 124.67, 122.31, 108.34, 78.62, 67.21, 26.77. Mass (*m*/*z*, r. i.): 354 (M^+, 100), 326 (50), 325 (88), 311 (67), 310 (75), 249 (29), 194 (68), 165 (86). Anal. Calcd. for $C_{23}H_{18}N_2O_2$ C, 77.95; H, 5.12; N, 7.90. Found: C, 77.55; H, 5.43; N, 7.70.

3-Benzhydryl-5,5-diphenyl-1′-methylspiro[1,3-oxazolidin-2,3′-indolin]-4,2′-dione (6). Mp: 202–204°C; IR (KBr, cm^{-1}): 2928, 1732, 1616, 1469, 1327; ^{1}H-NMR ($CDCl_3$, δ ppm): 7.69–7.64 (m, 4H), 7.39–7.02 (m 17H), 6.80 (t, 1H), 6.60 (d, 2H), 5.61 (s, 1H, methine), 2.94 (s, 3H, methyl); ^{13}C-NMR ($CDCl_3$, δ ppm): 171.5, 170.5, 144.0, 141.4, 140.9, 137.5, 137.1, 131.6, 129.6, 128.5, 128.2, 128.1, 128.0, 127.9, 127.87, 127.7, 127.5, 127.4, 126.6, 126.2, 124.6, 123.0, 108.7, 91.7, 85.9, 62.1, 26.3; Mass (*m*/*z*, r. i.): 536 (M^+, 5), 375 (68. M^+-1-methylindolinone-O), 341 (24), 314 (12), 237 (34), 167 (100), 152 (22), 105 (24), 77 (15). Anal. Calcd. for $C_{36}H_{28}N_2O_3$: reqd. C, 80.58; H, 5.26; N, 5.22. Found: C, 80.20; H, 5.52; N, 5.00.

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