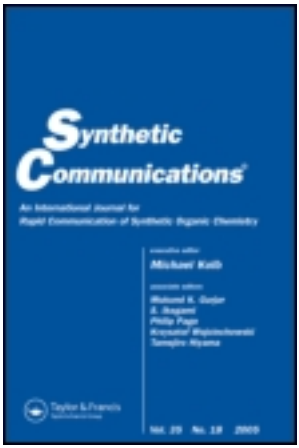

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A Regioselective Synthesis of Tetrahydrobenzodiazepin-5-ones via the Schmidt Rearrangement of Quinolones

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ABSTRACT

The regioselective synthesis of 2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepin-5-ones by the Schmidt rearrangement of 1,2,3,4-tetrahydro-4-quinolones with oxygen substituents at C-8 is described.

Key Words: Benzodiazepines; Schmidt rearrangement; Quinolones; Ketones; Hydrazoic acid.

INTRODUCTION

The wide range of biological activities displayed by benzodiazepines have attracted attention in synthetic organic chemistry.[1–3] In the context of a

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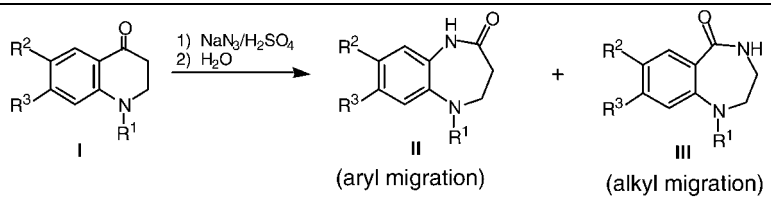
project to obtain heterocyclic quinones[4,5] with the quinone moiety fused to a diazepine ring we became interested in the Schmidt rearrangement of quinolones.

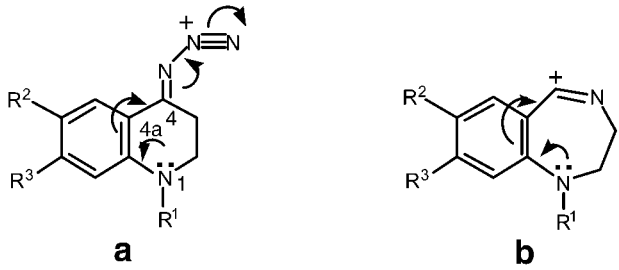
The Schmidt reaction on 1,2,3,4-tetrahydro-4-quinolones (**I**) was first reported by Ittyerah and Mann[6] to give a mixture of 2,3,4,5-tetrahydro-1,5-benzodiazepin-2-ones (**II**) and 2,3,4,5-tetrahydro-1,4-benzodiazepin-5-ones (**III**) through migration of an aryl or an alkyl group, respectively. When the aromatic ring of **I** has no substituent, the alkyl migration predominates, affording 1,4-benzodiazepin-5-ones (**III**) as the major isomers. The presence, on the aromatic system, of electron-donating or electron-withdrawing substituents seems to have little influence on the ratio of regioisomers. On the other hand, a reversal of regioselectivity is observed when the nitrogen atom bears an electron-withdrawing substituent, such as an acetyl group. In this case, the aryl migration prevails, leading mainly to 1,5-benzodiazepin-2-ones (**II**) (Table 1).[7]

The generally accepted mechanism for the Schmidt rearrangement involves formation of *syn*- and *anti*-iminodiazonium ions, followed by migration of the *anti*-substituent.[8] In addition, it has been suggested that the lone pair electron of the heterocyclic nitrogen plays an important role in the Schmidt rearrangement of tetrahydroquinolones. When the iminodiazonium ion is formed, delocalization of the nitrogen lone pair electron in Sch. 1(a) would result in a partial double bond formation between C-4a and C-4, inhibiting the aryl migration. Moreover, the lone pair electron delocalization

Table 1. Migratory tendencies in the Schmidt reaction of tetrahydroquinolones.[7]



	Benzodiazepine isomer ratio	
Tetrahydroquinolones	**II** (1,5-isomer)	**III** (1,4-isomer)
Ia $R^1 = H$, $R^2 = H$, $R^3 = H$	20	80
Ib $R^1 = H$, $R^2 = H$, $R^3 = OMe$	30	70
Ic $R^1 = H$, $R^2 = Cl$, $R^3 = H$	35	65
Id $R^1 = Ac$, $R^2 = H$, $R^3 = H$	95	5
Ie $R^1 = Ac$, $R^2 = Cl$, $R^3 = H$	90	10
If $R^1 = Ac$, $R^2 = H$, $R^3 = OMe$	90	10



Scheme 1. Heterocyclic nitrogen participating in (a) inhibiting the aryl migration and (b) stabilizing the carbocation generated via the alkyl migration.

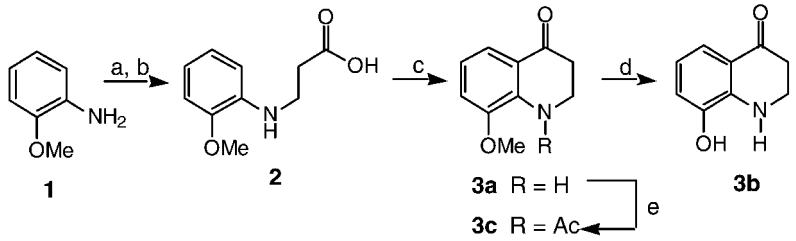
of nitrogen would stabilize the newly developing positive charge in Sch. 1(b), enhancing the alkyl migration (Sch. 1). In contrast, the presence of an acetyl group on the heterocyclic nitrogen, by reducing its resonance effect, favors the aryl migration.[9]

RESULTS AND DISCUSSION

In view to obtain precursors of benzodiazepinequinones via the Schmidt rearrangement, we synthesized 1,2,3,4-tetrahydro-4-quinolones **3** bearing an oxygenated substituent at the C-8 position. Thus, reaction of 2-methoxyaniline (**1**) with methyl acrylate (for a previous example of the reaction of anilines with methyl, acrylate see Ref.[10]) followed by basic hydrolysis gave 3-(2-methoxyphenylamino)propanoic acid (**2**) (for a previous report on the influence of steric and electronic effect on the Schmidt rearrangement, see Ref.[11]). Then, cyclization of **2** in polyphosphoric acid at 150°C gave tetrahydroquinolone **3a**, which on treatment with hydrobromic acid under reflux for 5 hr afforded phenol **3b** in good yield. Reaction of **3a** with acetic anhydride and pyridine yielded acetylquinolone **3c** (Sch. 2).

Then, the Schmidt rearrangement of compound **3** was studied using sodium azide and sulfuric acid. Thus, tetrahydroquinolone **3a** gave a mixture of 1,5-benzodiazepin-2-one **4a** and 1,4-benzodiazepin-5-one **5a** in the ratio of 20 : 80. The hydroxy derivative **3b** afforded similarly **4b** and **5b** with a ratio of 31 : 69 (Table 2).

The structure of the 1,5-benzodiazepine isomers **4a** and **4b** was assigned from their respective ^{1}H-NMR spectral data. Thus, considering **4a**, the methylene protons adjacent to the carbonyl group (3-CH_2) are shifted to high field ($\delta = 2.77$ ppm). On the other hand, for 1,4-benzodiazepinone **5a**, the same protons showed a multiplet at $\delta = 3.55$ ppm due to their deshielding



Scheme 2. Reagents and conditions: (a) methyl acrylate, acetic acid 145°C, 24 hr; (b) KOH, EtOH, reflux, 2 hr; AcOH, 75%; (c) polyphosphoric acid, 150°C, 58%; (d) HBr, reflux, 5 hr, 82%; (e) acetic anhydride, pyridine, room temperature, 24 hr, 87%.

by the adjacent nitrogen atom. The structures for **4b** and **5b** were determined in a similar manner.

The above results agree with the previous work on the Schmidt reaction of tetrahydroquinolones, confirming that a methoxy or a hydroxy group on the aromatic ring has a little influence on the regioisomeric ratio.[7] The predominant regioisomer is the 1,4-benzodiazepinone (**5a** or **5b**) produced via an alkyl migration.

Finally, considering the Schmidt rearrangement of *N*-acetylquinolone **3c** and following the literature data, the expected 1,5-benzodiazepinone **4c** via an aryl migration was not obtained. The reaction afforded only the 1,4-benzodiazepinone **5c** (alkyl migration) in 90% yield. The unexpected regioselectivity observed in the rearrangement of *N*-acetylquinolone **3c** is probably due to a steric interaction between the methoxy group at C-8 and the N-acetyl group (for a previous report on the influence of steric and electronic effect on the Schmidt rearrangement, see Ref.[11]).

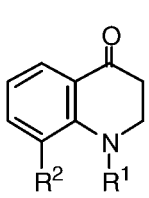
Another useful difference that confirms the structure of each isomer is that the ^{1}H-NMR signal of the 6-H proton for the 1,4-isomers (**5a**, **5b**, **5c**) is highly deshielded ($\delta = 7.30-7.61$ ppm) by the peri-carbonyl group, while for the 1,5-isomers (**4a**, **4b**) the ^{1}H-NMR signal of the 9-H proton is shielded ($\delta = 6.57-6.60$ ppm), since the amide moiety is connected to the aromatic ring by the nitrogen atom.

In conclusion, we have described a simple access to 1,4-benzodiazepinones **5** using the Schmidt reaction on 1,2,3,4-tetrahydro-4-quinolones **3** bearing oxygenated substituents at C-8.

EXPERIMENTAL

Melting points were determined with a Meltemp apparatus and are not corrected. IR spectra were obtained on a Bruker Model Vector 22

Table 2. Results of the Schmidt rearrangement of 1,2,3,4-tetrahydro-4-quinolones **3**.



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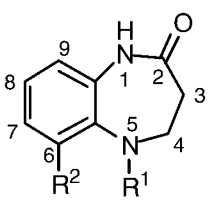

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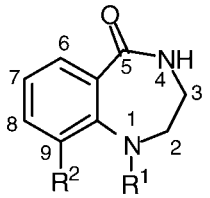

5

Quinolone	R^1	R^2	Benzodiazepinone	Overall yield (%)	Ratio **4**/**5**	^{1}H-NMR 3-CH_2	9-H (**4**)	3-CH_2	6-H (**5**)
3a	H	OMe	**4a**, **5a**	88	20/80	2.77	6.57	3.55	7.61
3b	H	OH	**4b**, **5b**	70	31/69	2.55	6.60	3.27	7.32
3c	Ac	OMe	**5c**	90	0/100			2.90	7.30

spectrophotometer. NMR spectra (^{1}H and ^{13}C) were recorded on a Bruker AM-200 spectrometer 200 (200 and 50 MHz), using TMS as internal reference. Column chromatography was performed on silica gel Merck 60 (70–230 mesh). Elemental analyses were performed on a Fison EA 1108 CHNS-O analyzer.

2-(2-Methoxyphenyl)propanoic acid (2). A mixture of *o*-anisidine (20 g, 0.162 mol), methyl acrylate (17.2 g, 0.2 mol), and acetic acid (6.0 mL) was heated at 145°C for 24 hr. The reaction mixture was concentrated and the residue was slowly treated with a solution of potassium hydroxide (11.4 g, 0.2 mol) in ethanol (70 mL). After heating at reflux for 2 hr, the solution was cooled, diluted with water (200 mL), and extracted with ethyl ether (3 × 100 mL). The aqueous solution was acidified with acetic acid and extracted with chloroform (3 × 100 mL). The combined organic phases were washed with water (50 mL) and then dried ($MgSO_4$) and concentrated. The crude product was crystallized from benzene to give (75%) of acid **2**, m.p. 87–88°C (87–88°C).[a]

1,2,3,4-Tetrahydro-8-methoxyquinolin-4-one (3a). Obtained in 58% yield from acid **2** (10 mmol) according to the general method of Atwal et al.[12]

1,2,3,4-Tetrahydro-8-hydroxyquinolin-4-one (3b). A solution of 1,2,3,4-tetrahydro-8-methoxyquinolin-4-one **3a** (1.0 g, 5.65 mmol) in aqueous hydrobromic acid (48%, 25 mL) was heated to reflux for 5 hr. The reaction mixture was concentrated under reduced pressure, the residue was poured into a solution of saturated sodium carbonate and extracted with ethyl acetate (4 × 25 mL). The extract was dried ($MgSO_4$), the solvent evaporated under vacuum, and the crude product was purified by column chromatography using methylene chloride–ethyl acetate (1 : 1) to yield phenol **3b** (0.75 g, 82%), m.p. 223–224°C. Anal. calcd for $C_9H_9NO_2$(163.18): C, 66.25; H, 5.56; N, 8.58. Found: C, 65.95; H, 5.29; N, 8.54. IR (KBr): 3400, 1640 cm^{-1}; ^{1}H-NMR (acetone-d_6): 2.6–2.7 (1H, m, 3-H), 3.1–3.2 (2H, m, 2-H), 3.6–3.7 (1H, m, 3-H), 5.60 (1H, br s, NH), 6.55 (1H, t, $J = 8.0$ Hz, 6-H), 6.94 (1H, dd, $J = 8.0$ and 1.3 Hz, 7-H), 7.32 (1H, dd, $J = 8.0$ and 1.3 Hz, 5-H), 8.98 (1H, br s, OH); ^{13}C-NMR (acetone-d_6): 39.1, 43.0, 117.0, 118.5, 118.8, 120.6, 144.4, 145.9, and 193.9.

1,2,3,4-Tetrahydro-8-methoxy-*N*-acetyl-4-quinolone (3c). Acetic anhydride (5 mL) was added to a solution of quinolone **3a** (0.5 g, 2.8 mmol) in pyridine (3 mL) and the mixture was left overnight at room temperature. The reaction mixture was poured into ice-water and was extracted with methylene

[a]This compound was obtained previously by reaction of *o*-anisidine with propiolactone, see reference.[12]

chloride (2 × 25 mL). The organic extract was washed with 5% sodium carbonate solution, then water, and dried ($MgSO_4$). The solvent was removed and the residue was purified by column chromatography using methylene chloride-ethyl acetate (20 : 1) to give compound **3c** (0.52 g, 87%) as an oil. Anal. calcd for $C_{12}H_{13}NO_3$(219.24): C, 65.74; H, 5.98; N, 6.39. Found: C, 65.81; H, 6.16; N, 6.30. IR (KBr): 1675, 1645 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 2.13 (s, 3H, CH_3), 2.75 (2H, m, 3-H), 3.4 (1H, m, 2-H), 3.87 (3H, s, OCH_3), 5.0 (1H, m, 2-H), 7.12 (1H, dd, $J = 8.2$ and 1.4 Hz, 7-H), 7.22 (1H, t, $J = 8.2$ Hz, 6-H), 7.56 (1H, dd, $J = 8.2$ and 1.4 Hz, 5-H); ^{13}C-NMR ($CDCl_3$): 21.9, 40.1, 44.1, 55.9, 117.2, 119.3, 127.0, 128.5, 134.1, 152.4, 171.1, and 194.9.

Schmidt Expansion on 1,2,3,4-Tetrahydroquinolin-4-ones. General Procedure. Concentrated sulfuric acid (2.5 mL) was added slowly to a stirred solution of quinolone **3** (500 mg) in chloroform (5 mL) at 0°C, then sodium azide (500 mg) was added gradually over 30 min. After 3 hr at room temperature, the reaction mixture was cooled and then neutralized with 10% aqueous solution of $NaHCO_3$ and extracted with ethyl acetate. The extract was dried with $NaSO_4$ and filtered. The filtrate was chromatographed on a silica gel column with ethyl acetate/methylene chloride.

6-Methoxy-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-2-one (4a) and 9-methoxy-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepin-5-one (5a). From quinolone **3a** obtained in order of elution, **4a** (18%), R_F 0.50 (ethyl acetate), m.p. 140–141°C. Anal. calcd for $C_{10}H_{12}N_2O_2$ (192.22): C, 62.49; H, 6.29; N, 14.57. Found: C, 62.20; H, 6,10; N, 14.50. IR (KBr): 3365, 3310, 3170, 1669 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 2.77 (2H, t, $J = 5.7$ Hz, 3-CH_2), 3.62 (2H, t, $J = 5.7$ Hz, 4-CH_2), 3.85 (3H, s, OCH_3), 4.4 (1H, br s, NH), 6.53 (1 H, dd, $J = 8.0$ and 1.5 Hz, 7-H), 6.57 (1H, dd, $J = 8.0$ and 1.5 Hz, 9-H), 6.71 (1H, t, $J = 8.0$ Hz, 8-H), and 8.16 (1H, br s, HNC═O); ^{13}C-NMR ($CDCl_3$): 37.1, 45.0, 55.9, 106.0, 114.5, 118.5, 125.2, 128.9, 149.3, and 174.0; and **5a** (70%), R_F 0.23 (ethyl acetate), m.p. 201–202°C. Anal. calcd for $C_{10}H_{12}N_2O_2$ (192.22): C, 62.49; H, 6.29; N, 14.57. Found: C, 62.30; H, 6,15; N, 14.45; IR (KBr): 3195, 1655 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 3.55 (4H, m, 2-CH_2 and 3-CH_2), 3.83 (3H, s, OCH_3), 4.3 (1H, br s, NH), 6.66 (1H, t, $J = 8.0$ Hz, 7-H), 6.82 (1H, dd, $J = 8.0$ and 1.2 Hz, 8-H), 7.42 (1H, br s, HNC═O), and 7.61 (1H, dd, $J = 8.0$ and 1.2 Hz, 6-H); ^{13}C-NMR ($CDCl_3$): 42.3, 48.3, 56.0, 111.6, 115.8, 116.6, 124.7, 136.8, 147.3, and 172.0.

6-Hydroxy-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-2-one (4b) and 9-Hydroxy-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepin-5-one (5b). From quinolone **3a** obtained in order of elution, **4b** (22%), R_F 0.30 (ethyl acetate), m.p. 219–220°C. Anal. calcd for $C_9H_{10}N_2O_2$(178.19): C, 60.67; H, 5.66; N, 15.72. Found: C, 60.40; H, 5.35; N, 15.50. IR (KBr): 3376, 3177, 1646 cm^{-1}; ^{1}H-NMR (DMSO-d_6): 2.55 (2H, m, 3-CH_2), 3.53 (2H, m, 4-CH_2), 4.94 (1H, br s, NH), 6.6 (3H, m, ArH), 9.38 (1H, s, OH) and 9.63

(1H, br s, HNC═O); ^{13}C-NMR (DMSO-d_6): 36.8, 44.1, 109.3, 112.9, 117.4, 126.2, 128.1, 146.6, and 172.8; and **5b** (48%), R_F 0.13 (ethyl acetate), m.p. 146–147°C. Anal. calcd for $C_9H_{10}N_2O_2$ (178.19): C, 60.67; H, 5.66; N, 15.72. Found: C, 60.35; H, 5.40; N, 15.45. IR (KBr): 3423, 3267, 3188, 1641 cm^{-1}; ^{1}H-NMR (DMSO-d_6): 3.27 (2H, m, 3-CH_2), 3.46 (2H, m, 2-CH_2), 5.80 (1H, s, NH), 6.47 (1H, t, $J = 8.0$ Hz, 7-H), 6.80 (1H, dd, $J = 8.0$ and 1.5 Hz, 8-H), 7.32 (1H, dd, $J = 8.0$ and 1.5 Hz, 6-H), 8.00 (1H, br s, HNC═O), and 9.74 (1H, br s, OH); ^{13}C-NMR (DMSO-d_6): 41.4, 47.9, 114.42, 114.47, 116.7, 122.8, 136.2, 144.7, and 170.1.

1-Acetyl-9-methoxy-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepin-5-one (5c). From quinolone **3a** was obtained compound **5c** (90%), m.p. 150–151°C. Anal. calcd for $C_{12}H_{14}N_2O_3$ (234.26): C, 61.53; H, 6.02; N, 11.96: Found: C, 61.60; H, 6.30; N, 12.15. IR (KBr): 3190, 1675, 1650 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 2.9 (2H, m, 3-CH_2), 3.2 (1H, m, 2-CH_2), 3.86 (3H, s, CH_3), 4.4 (1H, dt, $J = 5.7$ and 12.7 Hz, 2-H), 7.15 (2H, dd, $J = 1.1$ and 8.0 Hz, 8-H), 7.30 (2H, dd, $J = 1.1$ and 8.0 Hz, 6-H), 7.48 (1H, t, $J = 8.0$ Hz, 7-H), and 8.20 (1H, br s, HNC═O); ^{13}C-NMR ($CDCl_3$): 21.1, 38.1, 47.8, 55.9, 114.6, 120.1, 125.7, 129.7, 135.1, 154.6, 169.4, and 170.2.

ACKNOWLEDGMENT

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