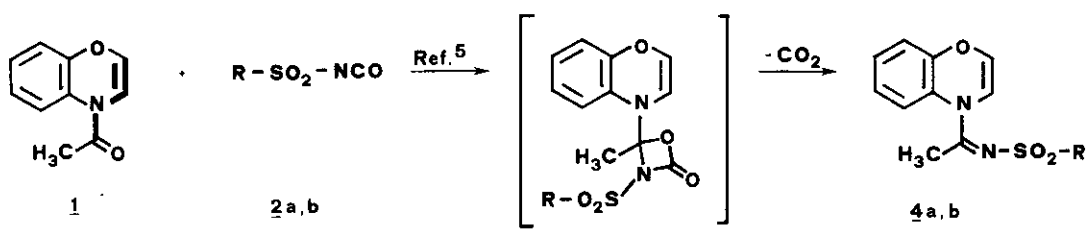
A NEW SYNTHESIS OF IMIDAZO[5,1-c][1,4]BENZOXAZINES VIA THEIR CORRESPONDING REISSERT-TYPE COMPOUNDS[1]

Herbert Bartsch*, Otto Schwarz, and Gustav Neubauer
Institute of Pharmaceutical Chemistry, University of Vienna,
A-1090 Vienna, Währinger Straße 10, Austria

Abstract - A new synthesis of imidazo[5,1-c][1,4]benzoxazines via Reissert-type compounds, obtained from 2-(2-aminophenoxy)-1,1-dimethoxyethane, is described.

In the course of our investigations concerning the synthesis of tricyclic oxaza-heterocycles[2,3], we became interested in a facile access to unsaturated imidazo-[5,1-c][1,4]benzoxazines. A tedious synthesis of this heterocyclic system, which is of potential pharmacological interest, has been described only once in literature[4].

Previously[5], we reported the formation of amidines 4a,b by reaction of 1 with sulphonyl isocyanates 2a,b (Scheme 1). Supposedly, the mechanism of this conversion involves a [2+2]cycloaddition leading to the unstable intermediate 3a,b, which was transformed spontaneously into the corresponding amidines 4a and 4b, respectively. This mechanistic interpretation rests on the fact, that the N-acylcarbonyl function in 1 as part of an enamide structure, possesses considerable electrophilic character and hence, is readily reacted with nucleophiles.

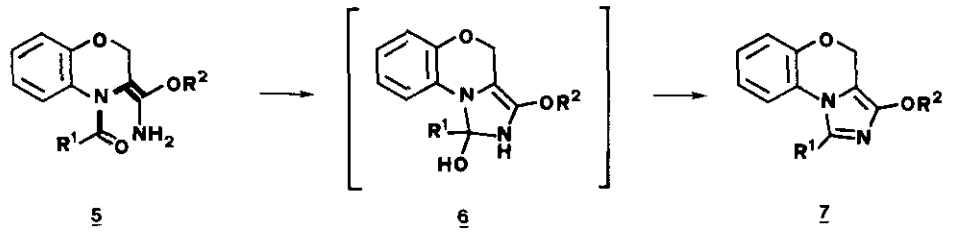


1 2a,b 3a,b 4a,b

a R=Cl
b R=4-Me-Ph

Scheme 1

According to these considerations the imido ether 5, which contains an exocyclic enamide-moiety, should be cyclized by intramolecular nucleophilic addition and successive dehydration via intermediate 6 into the target heterocycle 7. Variation of R^1 and R^2 should offer access to various derivatives of 7 (Scheme 2).

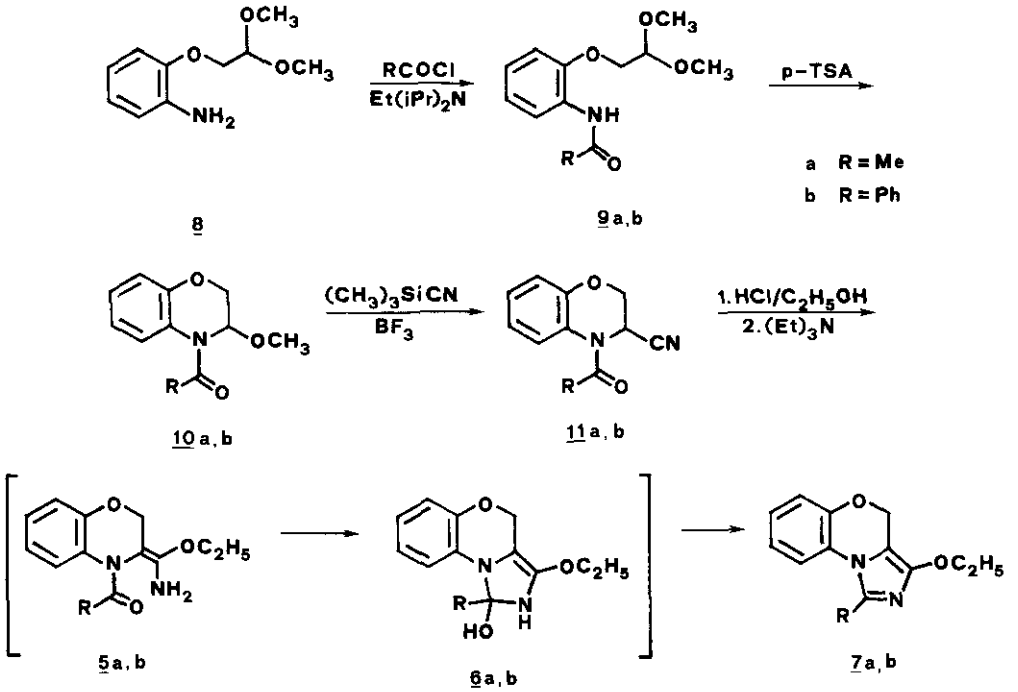


5 6 7

Scheme 2

Readily available synthons for the synthesis of imido ether 5 are the Reissert-type compounds 11a,b.

Dihydro-1,4-benzoxazine-3-carbonitriles 11a,b are obtained via a modified three-step synthesis[6-8], involving: acylation of 2-aminophenoxyacetal 8[9] and cyclization of the resulting amides 9a,b to the dihydrobenzoxazines 10a[8],b, which were treated with trimethylsilylcyanide yielding 11a[8],b (Scheme 3). The described modification enables an easier workup and a more facile purification of the products.



8 9a,b

a R = Me
b R = Ph

10a,b 11a,b

5a,b 6a,b 7a,b

Scheme 3

Treatment of 11a,b with ethanol/gaseous hydrochloric acid and successive neutralization of the reaction solution with triethylamine afforded 5a,b, which cyclised on standing at room temperature into the expected imidazobenzoxazines 7a,b, whose structures were confirmed by spectroscopic means (Scheme 3). These results describe a new synthetic application of Reissert-type compounds.

EXPERIMENTAL

All melting and boiling points are uncorrected. Mass spectra were recorded on a Varian MAT-311 instrument and ^{1}H-NMR spectra on a Varian EM-390 (90 MHz) spectrometer.

General Procedure for the Formation of 2-(2-Acylaminophenoxy)-1,1-dimethoxyethanes 9; (Modification to References[6,7]) To a mixture of the acetal 8[9] (1.97 g, 10 mmol) and ethyldiisopropylamine (1.55 g, 12 mmol) in ether (50 ml), a solution of acyl chloride (10 mmol) in ether (10 ml) was added dropwise at 20°C. After 2 h the precipitation was filtered off and the etheral solution was washed with 2N HCl, a saturated solution of $NaHCO_3$ and water, dried over Na_2SO_4, filtered and evaporated. The residue was distilled under reduced pressure.

2-(2-Acetylaminophenoxy)-1,1-dimethoxyethane (9a): from 8 with acetyl chloride (0.785 g) 2.27 g (95%) of 9a were obtained; colourless needles; mp (from *n-pentane*) 53-54°C; bp 115°C, 0.005 mmHg; MS: m/z 239 (M^+); ^{1}H-NMR ($CDCl_3$/TMS): δ 2.14 (s, 3H, CH_3-CO), 3.43 (s, 6H, 2x CH_3-O), 4.04 (d, J = 6 Hz, 2H, CH_2-O), 4.65 (t, J = 6 Hz, 1H, CH), 6.86-7.00 (m, 3H, aromat.), 8.0 (broad s, 1H, NH), 8.21-8.41 (m, 1H, aromat.) ppm; Anal. Calcd. for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.25; H, 7.21; N, 5.73.

2-(2-Benzoylaminophenoxy)-1,1-dimethoxyethane (9b): from 8 with benzoyl chloride (1.406 g) 2.41 g (80%) of 9b were obtained; white crystals; mp 36-37°C; bp 190°C, 0.01 mmHg; MS: m/z 301 (M^+); ^{1}H-NMR ($CDCl_3$/TMS): δ 3.46 (s, 6H, 2x CH_3-O), 4.08 (d, J = 6 Hz, 2H, CH_2-O), 4.82 (t, J = 6 Hz, 1H, CH), 6.88-7.15 (m, 3H, aromat.), 7.35-7.68 (m, 3H, aromat.), 7.79-8.12 (m, 2H, aromat.), 8.49-8.89 (m, 1H, aromat.), 8.9 (broad s, 1H, NH) ppm; Anal. Calcd. for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 68.05; H, 6.37; N, 4.67.

General Procedure for the Formation of 4-Acyl-3,4-dihydro-3-methoxy-2H-1,4-benzoxazines 10; (Modification to References[6,7]) The solution of 9 (10 mmol) and p-toluenesulphonic acid (p-TSA) (86 mg, 0.5 mmol) in toluene (150 ml) was heated at 75°C. The reaction was monitored by TLC (silica gel, toluene/ethyl

acetate 6:4). After completion of the reaction, the solution was washed with a saturated solution of $NaHCO_3$ and water, dried with Na_2SO_4, filtered and evaporated. The residue was purified by distillation under reduced pressure or by recrystallization.

4-Acetyl-3,4-dihydro-3-methoxy-2H-1,4-benzoxazine (10a): from 9a (2.39 g) 1.26 g (61%) of 10a were obtained; colourless oil; bp 110°C, 0.001 mmHg (ref.[8] 119°C, 0.005 mmHg).

4-Benzoyl-3,4-dihydro-3-methoxy-2H-1,4-benzoxazine (10b): from 9b (3.01 g) 1.75 g (65%) of 10b were obtained; white crystals; mp (from methanol) 126°C; MS: m/z 269 (M^+); ^{1}H-NMR ($CDCl_3$/TMS): δ 3.47 (s, 3H, CH_3-O), 4.38 and 4.62 (AB-part of an ABX-system, J_{AX} = 1.5 Hz, J_{BX} = 2 Hz, J_{AB} = 12 Hz, 2H, CH_2-O), 5.88 (X-part, 1H, CH-N), 6.55-6.72 (m, 2H, aromat.), 6.92-7.02 (m, 2H, aromat.), 7.32-7.58 (m, 5H, aromat.) ppm; Anal. Calcd. for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.36; H, 5.78; N, 4.95.

General Procedure for the Formation of 4-Acyl-3,4-dihydro-2H-1,4-benzoxazine-3-carbonitriles 11; (Modification to Reference[8]) To a solution of 10 (10 mmol) and BF_3 etherate (0.2 ml) in ether (80 ml), trimethylsilylcyanide (0.99 g, 10 mmol) was added dropwise at 20°C. After stirring for 24 h the addition of BF_3 etherate and trimethylsilylcyanide (same quantities as above) was repeated. After completion of the reaction (TLC control: silica gel, cyclohexane/ethyl acetate 7:3) the mixture was washed with a saturated solution of $NaHCO_3$ and water, dried with Na_2SO_4, filtered and evaporated. The solid residue was recrystallized.

4-Acetyl-3,4-dihydro-2H-1,4-benzoxazine-3-carbonitrile (11a): 10a (2.07 g) afforded 1.94 g (96%) of 11a; colourless needles; mp (from ethyl acetate) 90°C (ref.[8] 89°C).

4-Benzoyl-3,4-dihydro-2H-1,4-benzoxazine-3-carbonitrile (11b): 10b (2.69 g) afforded 2.51 g (95%) of 11b; pale yellow needles; mp (from methanol) 160°C; MS: m/z 264 (M^+); ^{1}H-NMR ($CDCl_3$/TMS): δ 4.46 and 4.77 (AB-part of an ABX-system, J_{AX} = 2 Hz, J_{BX} = 3 Hz, J_{AB} = 12 Hz, 2H, CH_2-O), 5.83 (X-part, 1H, CH-N), 6.62-6.82 (m, 2H, aromat.), 6.89-7.15 (m, 2H, aromat.), 7.32-7.68 (m, 5H, aromat.) ppm; Anal. Calcd. for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60. Found: C, 72.58; H, 4.71; N, 10.62.

General Procedure for the Formation of 1-Substituted 3-Ethoxy-4H-imidazo[5,1-c]-[1,4]benzoxazines 7 HCl gas (0.54 g, 15 mmol) was introduced to a solution

of 11 (10 mmol) in ethanol (30 ml) at 0°C. After standing for 48 h at 0°C the excess of HCl gas was removed by passing a stream of dry N_2 through the solution. After alkalisation with triethylamine the mixture was stirred for another 48 h. Ethanol was evaporated and the residue was dissolved in ether (50 ml) and a 5% solution of $NaHCO_3$ (30 ml). The separated etheral solution was washed with water, dried with Na_2SO_4, filtered and evaporated. The crude product was purified by preparative chromatography (7a: toluene/ethyl acetate 6:4, R_f = 0.23; 7b: cyclohexane/ethyl acetate 9:1, R_f = 0.70).

3-Ethoxy-1-methyl-4H-imidazo[5,1-c][1,4]benzoxazine (7a): from 11a (2.02 g) 0.99 g (43%) of 7a were obtained; pale yellow crystals; mp 170-175°C (decomposition); MS: m/z 230.1055 (M^+). $C_{13}H_{14}N_2O_2$ requires: 230.1057; ^{1}H-NMR ($CDCl_3$/TMS): δ 1.33 (t, J = 7 Hz, 3H, CH_3), 2.59 (s, 3H, CH_3), 4.22 (qu, J = 7 Hz, 2H, CH_2), 4.99 (s, 2H, CH_2), 6.96-7.37 (m, 4H, aromat.) ppm; Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.16. Found: C, 67.63; H, 5.98; N, 12.36.

3-Ethoxy-1-phenyl-4H-imidazo[5,1-c][1,4]benzoxazine (7b): from 11b (2.64 g) 1.31 g (45%) of 7b were obtained; pale yellow oil; bp 180°C, 0.001 mmHg (decomposition); MS: m/z 292.1212 (M^+). $C_{18}H_{16}N_2O_2$ requires: 292.1217; ^{1}H-NMR ($CDCl_3$/TMS): δ 1.38 (t, J = 7 Hz, 3H, CH_3), 4.31 (qu, J = 7 Hz, 2H, CH_2), 5.15 (s, 2H, CH_2), 6.68-7.11 (m, 4H, aromat.), 7.35-7.55 (m, 5H, aromat.) ppm; Anal. Calcd. for $C_{18}H_{16}N_2O_2$: C, 73.96; H, 5.52; N, 9.58. Found: C, 73.65; H, 5.36; N, 9.85.

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