Formation of Reissert Analogs from Benzimidazole and Use of Carboxylic Acids in a Retro-Reissert Reaction [1]

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Reissert analogs have been formed in high yields from benzimidazole using trimethylsilyl cyanide and chloroformates. A retro-Reissert reaction can be effected on the products, their carbon-2 alkylated derivatives and benzothiazole analogs, by treatment with hexanoic or benzoic acids.

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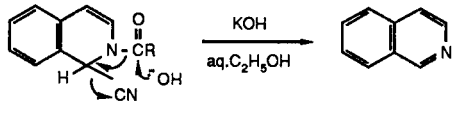
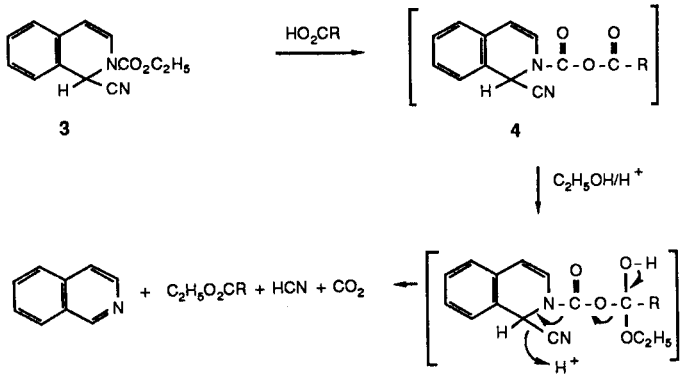
We recently reported the first syntheses of Reissert compounds from five-membered ring heterocycles benzothiazole and benzoxazole [2]. The method made use of trimethylsilyl cyanide as the source of cyanide in a single phase system. We have now applied the same approach to benzimidazole. Use of phenyl chloroformate as the acid chloride gave 2-cyano-2,3-dihydro-1,3-*bis*(phenoxycarbonyl)benzimidazole (**1a**) in 90% yield, and ethyl chloroformate gave analog **1b** similarly. The proton at carbon-2, which appears at δ 6.40 ppm in the nmr spectrum of **1b**, can be removed by use of lithium diisopropylamide. Alkylation of the anion of **1b** with methyl or ethyl iodide gave analogs **1c** and **1d** in good yield. Alkylation of benzothiazole Reissert analog **1e** with methyl iodide gave **1f** in 85% yield.

The conventional method to regenerate the fully aromatic heterocycle from a Reissert compound involves hydrolysis with potassium hydroxide in aqueous ethanol (Scheme 1) [3]. Treatment of 2-cyano-2,3-dihydro-3-methoxycarbonylbenzothiazole (**1e**) in this way, however, resulted in ring opening and the isolation of 2-aminobenzenethiol. We therefore examined the procedure of Tsizin and co-workers [4] who observed that when 2-ethoxycarbonyl-1,2-dihydroisoquinaldonitrile (**3**) or 1-ethoxycarbonyl-1,2-dihydroquinaldonitrile were heated with an equimolar quantity of hexanoic, cyclohexanecarboxylic or benzoic acid a retro-Reissert reaction occurs, giving isoquinoline or quinoline respectively, together with the ethyl ester of the acid used, hydrogen cyanide and carbon dioxide. The process is a transesterification and a possible mechanism is outlined (Scheme 2). If attack occurs at the carbonyl of the substrate **3** leading to the mixed anhydride **4**, alcoholysis would then lead to the products observed [5].

Scheme 1



Scheme 2



The Russian workers [4] did not report application of their method to alkylated Reissert compounds. We found that use of this procedure with Reissert analogs **1a, b, e** and alkylated derivatives **1c, d, f**, Scheme 3, efected the retro-Reissert reaction, giving the aromatic heterocycles **2** in isolated yields of 40-59%. The method therefore offers and improvement over yields give by the base hydrolysis route in some cases (See Table).

Scheme 3

	X	R^1	R^2
1a	NCO_2R^2	H	Ph
1b	NCO_2R^2	H	C_2H_5
1c	NCO_2R^2	CH_3	C_2H_5
1d	NCO_2R^2	C_2H_5	C_2H_5
1e	S	H	CH_3
1f	S	CH_3	CH_3

	X	R^1
2a	NH	H
2b	NH	CH_3
2c	NH	C_2H_5
2d	S	H
2e	S	CH_3

Table

Preparation of Compounds **2a-e**

Substrate	$R3CO_2H$ (2 equivalents) [a]	Product	Yield % [b]	Bp or Mp°C [c]
1a	$PhCO_2H$	**2a**	43 (37) [d]	178-179
1b	n-$C_5H_{11}CO_2H$	**2a**	40 (35) [d]	178-179
1b	$PhCO_2H$	**2a**	45	177-179
1c	n-$C_5H_{11}CO_2H$	**2b**	40 (42) [d]	168-170
1c	$PhCO_2H$	**2b**	50	168-170
1d	$PhCO_2H$	**2c**	40 (45) [d]	171-173
1e	n-$C_5H_{11}CO_2H$	**2d**	53 [e] (0) [f]	90/5 mm Hg
1e	$(CH_2)_5CHCO_2H$	**2d**	39 [g]	90/5 mm Hg
1e	$PhCO_2H$	**2d**	35 [h]	90/5 mm Hg
1f	n-$C_5H_{11}CO_2H$	**2e**	59 (35)	95/5 mm Hg

[a] Use of 1 equivalent of the acid gave inferior yields. [b] Values in parenthesis give precentage yields of **2** on hydrolysis of **1** with 15% potassium hydroxide/aqueous ethanol, reflux, 2 hours. [c] All products identical with commercial samples. [d] Base hydrolysis procedure carried out at room temperature, 10 hours. [e] 79% Based on recovered starting material. [f] *o*-Aminobenzenethiol (70%) isolated. [g] 70% Based on recovered starting material. [h] 50% Based on recovered starting material.

EXPERIMENTAL

All melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 177 grating spectrometer. Proton magnetic resonance spectra were determined with a Perkin-Elmer R32 instrument (90 MHz) or a Varian EM360A spectrometer (60 MHz). Microanalyses were determined by the Microanalytical Laboratory, University of Manchester. Column chromatography was carried out by the flash chromatography technique with Merck silica gel 60 for column chromatography (0.040-0.63 mm mesh).

Preparation of 2-Cyano-2,3-dihydro-1,3-*bis*(phenoxycarbonyl)benzimidazole (**1a**).

To a mixture of 0.83 g (7 mmoles) of benzimidazole stirred with 0.87 ml (7 mmoles) of trimethylsilyl cyanide and a catalytic amount (0.05 g) of aluminium chloride in 40 ml of anhydrous methylene chloride was added 2.18 g (14 mmoles) of phenyl chloroformate in 15 ml of methylene chloride over a period of 30 minutes. After an additional 48 hours of stirring, the solution was washed with water, 10% hydrochloric acid, 10% sodium hydroxide and water. The organic layer was dried over anhydrous magnesium sulphate. Concentration of the methylene chloride gave, after recrystallization from ethanol, 2.45 g (90%) of **1a**, mp 130-132°; ir (potassium bromide): 1735 (C=O), 1600 (C=C) cm^{-1}; pmr (deuteriochloroform): δ 7.92-7.00 (m, 14H), 6.95 (s, 1H, C-2).

Anal. Calcd. for $C_{22}H_{15}N_3O_4$: C, 68.6; H, 3.9; N, 10.9. Found: C, 68.8; H, 3.9; N, 10.9.

Preparation of other Reissert Analogs.

Using the procedure described above for the preparation of **1a**, the compounds **1b** and **1e** were prepared.

2-Cyano-1,3-*bis*(ethoxycarbonyl)-2,3-dihydrobenzimidazole (**1b**).

This compound 2-cyano-1,3-*bis*(ethoxycarbonyl)-2,3-dihydrobenzimidazole (**1b**) was obtained in 90% yield, mp 117-119°; ir (potassium bromide): 1710 (C=O), 1600 (C=C) cm^{-1}; pmr (deuteriochloroform): δ 7.65-6.65 (m, 4H), 6.40 (s, 1H, C-2), 4.35 (2 × q, 4H), 1.35 (2 × t, 6H).

Anal. Calcd. for $C_{14}H_{15}N_3O_4$: C, 58.1; H, 5.2; N, 14.5. Found: C, 58.25; H, 5.3; N, 14.4.

2-Cyano-2,3-dihydro-3-methoxycarbonylbenzothiazole (**1e**).

This compound 2-cyano-2,3-dihydro-3-methoxycarbonylbenzothiazole (**1e**) was obtained in 78% yield, mp 101-102° from ethyl acetate; ir (potassium bromide): 2225 (C≡N) 1735 (C=O) cm^{-1}; pmr (deuteriochloroform): δ 7.35-7.15 (m, 4H), 6.43 (s, 1H, C-2), 3.95 (s, 3H).

Anal. Calcd. for $C_{10}H_8N_2O_2S$: C, 54.5; H, 3.7; N, 12.7. Found: C, 54.5; H, 3.7; N, 12.65.

Alkylation of **1b**.

To a well stirred solution of 2 ml (14 mmoles) of anhydrous diisopropylamine and 6 ml (14 mmoles) of 15% *n*-butyllithium in hexane at −78°, under a nitrogen atmosphere was added 1.06 g (3.66 mmoles) of **1b** and 2.52 g (18 mmoles) of methyl iodide in 20 ml of anhydrous tetrahydrofuran. The stirred mixture was maintained at −78° for 1 hour and for an additional 24 hours at room temperature. The mixture was poured onto 500 g of crushed ice-water to give 0.71 g (63%) of 2-cyano-1,3-*bis*-(ethoxycarobonyl)-2,3-dihydro-2-methylbenzimidazole (**1c**). Recrystallization from ethyl acetate gave needles, mp 86-88°; ir (potassium bromide): 1712 cm^{-1} (C=O); pmr (deuteriochloroform): δ 7.67-6.66 (m, 4H), 4.35 (2 × q, 4H), 2.3 (s, 3H), 1.35 (2 × t, 6H).

Anal. Calcd. for $C_{15}H_{17}N_3O_4$: C, 53.4; H, 5.65; N, 13.9. Found: C, 53.5; H, 5.6; N, 13.9.

2-Cyano-1,3-*bis*-(ethoxycarbonyl)-2-ethyl-2,3-dihydrobenzimidazole (**1d**).

This compound was obtained by a similar procedure using ethyl iodide, 60% yield, mp 78-80° from ethanol.

Anal. Calcd. for $C_{16}H_{19}N_3O_4$: C, 60.55; H, 6.0; N, 13.2. Found: C, 60.7; H, 6.25; N, 13.2.

Alkylation of **1e**.

To a well stirred solution of 1.1 g (5 mmoles) of **1e** and 2.8 g (20 mmoles) of methyl iodide in 20 ml of anhydrous dimethylformamide at 0°, under a nitrogen atmosphere, was added 0.28 g (6 mmoles) of 50% sodium hydride in oil. The mixture was stirred at 0° for 1 hour and additional 24 hours at room temperature. The mixture was poured onto 50 g of ice-water, and the oil observed was extracted with dichloromethane (2 × 50 ml). The organic layer was washed thoroughly with water before drying over anhydrous magnesium sulphate. Evaporation of the solvent *in vacuo* gave an oil which was subjected to column chromatography using silica gel as an absorbent, an 15% ethyl acetate/petroleum ether (40/60) as eluent. 2-Cyano-2,3-dihydro-3-methoxycarbonyl-2-methylbenzothiazole (**1f**) was obtained in 85% yield, mp 63-65°; ir (potassium bromide): 2248 (C≡N), 1728 (C=O) cm^{-1}; pmr (deuteriochloroform): δ

7.95-7.10 (m, 4H), 4.02 (s, 3H, OCH_3), 2.25 (s, 3H, CH_3).

Anal. Calcd. for $C_{11}H_{10}N_2O_2S$: C, 56.4; H, 4.3; N, 12.0. Found: C, 56.65; H, 4.3; N, 11.9.

Conversion of Reissert Analogs (**1a-f**) to Aromatic Heterocycles **2a-e**.

A mixture of 2.7 mmoles of the Reissert analog **1** and 5.4 mmoles of the acid (hexanoic, cyclohexanecarboxylic or benzoic - see Table) was heated at an oil bath temperature of 130-140° for 4 hours. The reaction mass was dissolved in 30 ml of chloroform and washed with 50 ml of 20% sodium hydroxide. The chloroform was extracted with 50 ml of 50% hydrochloric acid and this acid layer was subsequently neutralised with sodium hydroxide solution. The neutralised solution was extracted with 2 × 50 ml of chloroform and dried over anhydrous magnesium sulphate. Concentration of the solvent gave the aromatic heterocycle **2**. The results of this conversion are summarized in the Table.

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