Pergamon

Tetrahedron 54 (1998) 9519–9528

TETRAHEDRON

The Synthesis and Chemical Reactivity of 3-Chloro-6-(2-Pyrrolyl)Pyridazine.

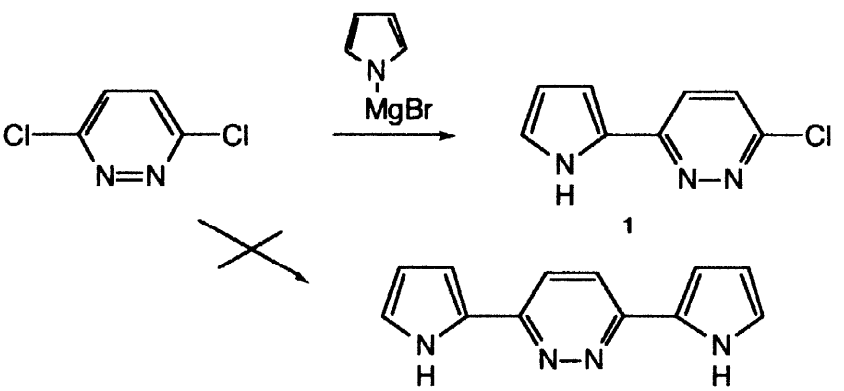
R. Alan Jones* and Alexander P. Whitmore

School of Chemical Sciences, University of East Anglia, Norwich NR4 7TJ UK

Received 5 November 1997; revised 20 November 1997; accepted 29 May 1998

Abstract: 3,6-Dichloropyridazine and 1-alkyl-3,6-dichloropyridazinium cations react with pyrrolylmagnesium bromide to produce 3-chloro-6-(2-pyrrolyl)pyridazine. Further reaction with other nucleophiles is slow, but is enhanced by quaternisation of the 2-N atom. 3,6-Di(2-pyrrolyl)pyridazine could not be obtained by this route. © 1998 Elsevier Science Ltd. All rights reserved.

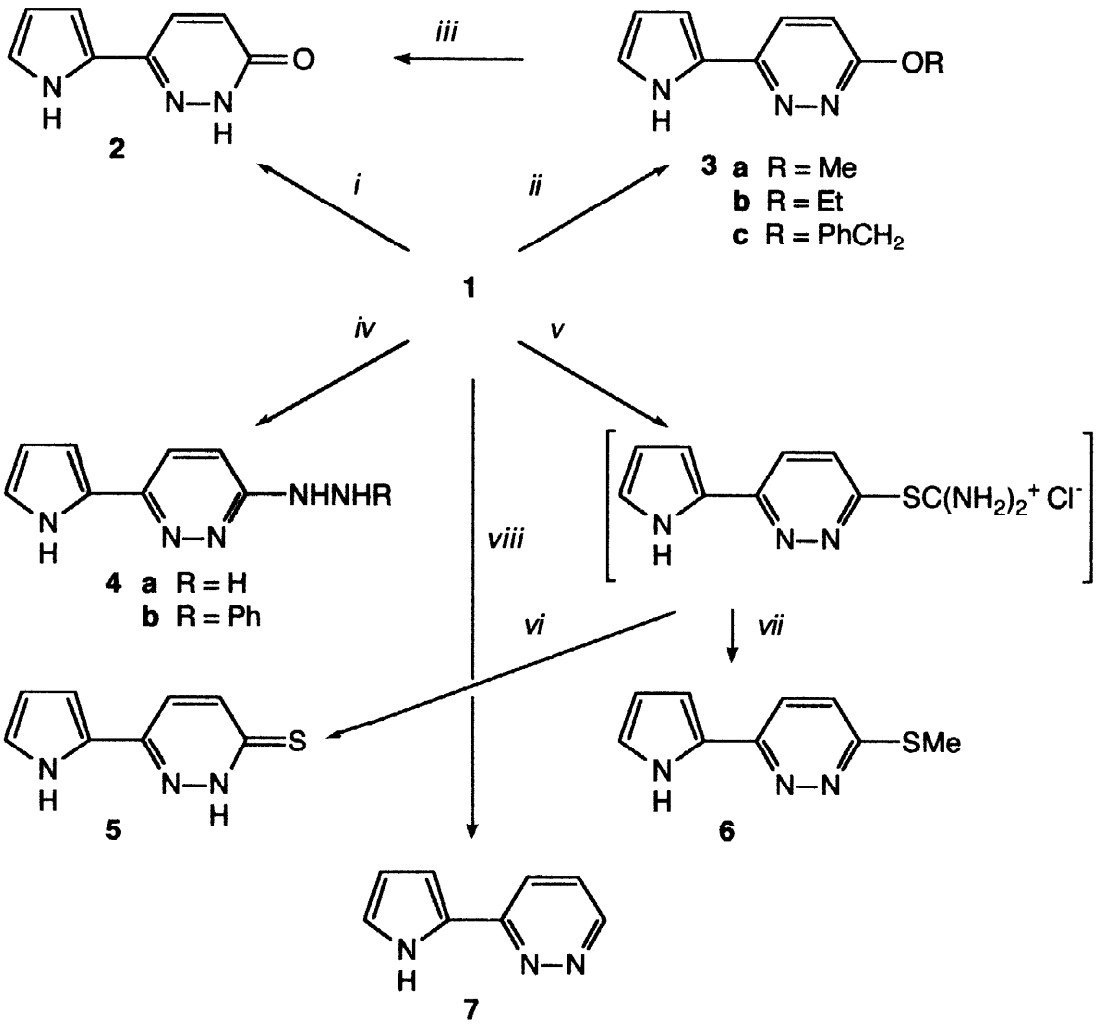
In continuation of our studies[1-3] of extended heterocyclic systems with potential semi-conductivity and non-linear optical properties, we sought to prepare 3,6-di(2-pyrrolyl)pyridazine and oligomeric pyrrolylpyridazines. Extension of the Stetter protocol used in the previous work[1-3] was unsuccessful for the pyridazine analogues, either because of the poor accessibility of suitable formylpyridazines or because the reaction between pyrrolylbutan-1,4-diones[4] with hydrazine only gave a complex mixture of products from which the pyridazine could not be isolated [*cf.* ref. 5]. It has been reported that 3-chloro-6-(3-indolyl)pyridazine can be obtained from the reaction of indolylmagnesium bromide and 3,6-dichloropyridazine.[6] Using an analogous route, we hoped to prepare 3,6-di(2-pyrrolyl)pyridazine, but, in spite of several modified procedures, we succeeded in isolating only 3-chloro-6-(2-pyrrolyl)pyridazine **1** (Scheme 1). Interestingly, 1-methyl-2-pyrrolyl lithium failed to react with 3,6-dichloropyridazine to produce the 1-methyl-2-pyrrolyl analogue of **1** and all attempts to react **1** further with heteroaryl Grignard reagents or with heteroaryl lithium compounds, such as 2-thienyl lithium or 1-methyl-2-pyrrolyl lithium failed.



With best wishes to Professor Alan Katritzky, FRS, on the occasion of his 70th birthday.

PII: S0040-4020(98)00513-4

In view of the failure of **1** to react further with the pyrrolyl Grignard reagent, it was of interest to explore the reactivity of **1** with other nucleophiles. Surprisingly, the reaction of **1** with hydroxide ion to yield 6-(2-pyrrolyl)pyridazin-3-one **2** was only effective in the presence of a phase-transfer catalyst. In the absence of such a catalyst no reaction occurred even under extremely vigorous conditions. The pyridazinone could also be obtained in good yield by hydrogenolysis of the corresponding 3-benzyloxy derivative or by demethylation of the 3-methoxy compound.

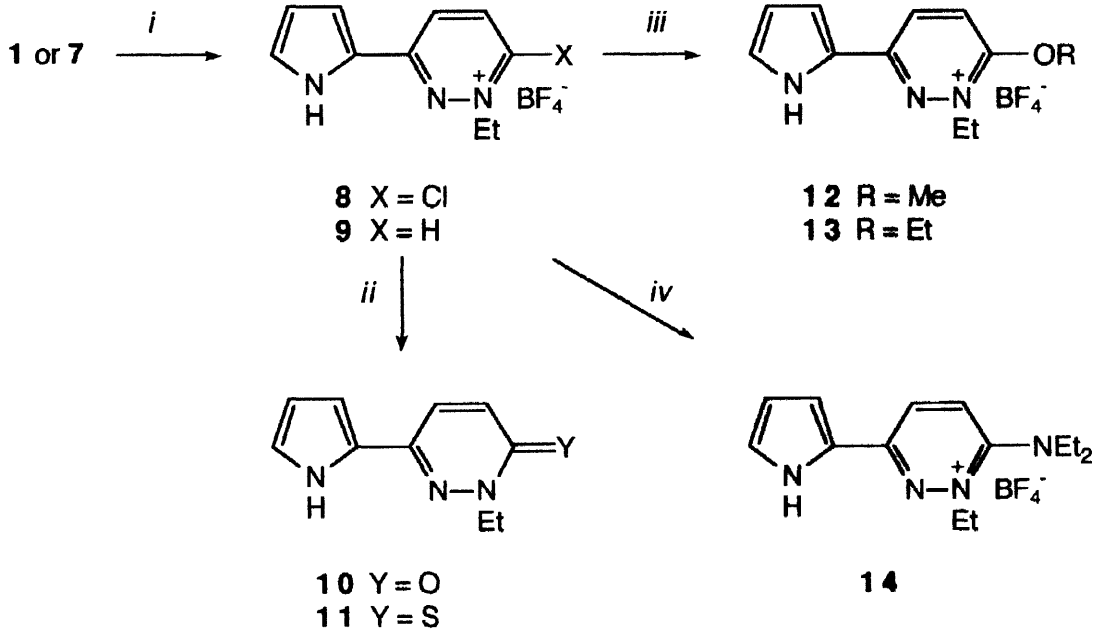


i 50% aq. NaOH, *n*-$Bu_4N^+Cl^-$, dichlorobenzene, 100°C. *ii* reflux RONa/ROH. *iii* R = $PhCH_2$: H_2 Pd/C. R = Me: *n*-BuLi and Ph_2PH in THF. *iv* reflux NH_2NH_2 in ethanol or *n*-BuLi/$PhNHNH_2$ in ether. *v* thiourea in *n*-butanol, 117°C. *vi* conc. aq. NH_3, 20°C. *vii* 20% aq. NaOH, $PhCH_2NEt_3^+Cl^-$, MeI, 42°C. *viii* HCO_2NH_4, Pd/C in methanol.

In contrast with the poor reaction of **1** with hydroxide ion, reaction occurred readily with alkoxide ions to yield the corresponding 3-alkoxypyridazines **3** but, whereas **1** reacted readily with hydrazines to produce the corresponding hydrazino compounds **4**, ammonia and primary and secondary amines failed to react with **1**. All attempts to produce the aminopyridazines, either by direct reaction with the amine or with potassium phthalimide, or by cleavage of the hydrazino derivatives failed. Reaction of **1** with thiourea, followed by a hydrolytic work-up produced the pyridazin-3-thione **5**, while reaction of the intermediate isothiouronium salt

with iodomethane in the presence of a phase-transfer catalyst gave the 3-methylthio derivative **6**. All reactions of **1** with carbon nucleophiles under normal conditions failed. Hydride hydrogenolysis of **1** using ammonium formate in the presence of palladium on carbon successfully produced the parent pyrrolylpyridazine **7** in excellent yield.

The simple pyrrolylpyridazine systems were not readily quaternised using standard conditions with iodomethane (*cf.* quaternisation of 2-(2-pyridyl)pyridines[1,3]), but reaction of **1**, **7**, **3a** and **3b** with the more reactive triethyloxonium tetrafluoroborate gave exclusively the 3-substituted 2-ethyl-6-(2-pyrrolyl)pyridazinium salts **8**,**9**,**12** and **13**, respectively. These observations, which we confirmed by X-ray crystallographic analysis,[7] are in accord with previous reports which record that quaternisation of the pyridazine ring is controlled by steric and inductive effects of substituents at the 3/6-positions and that, although both 1- and 2-alkylated products may be obtained, the 1-alkylpyridazinium salts predominate with bulky and/or -I substituents at the 3-position. Our results are also in keeping with our earlier observations that 3-(2-pyrrolyl)pyridines are quaternised *ca.* 175 times more readily than are 2-(2-pyrrolyl)pyridines.



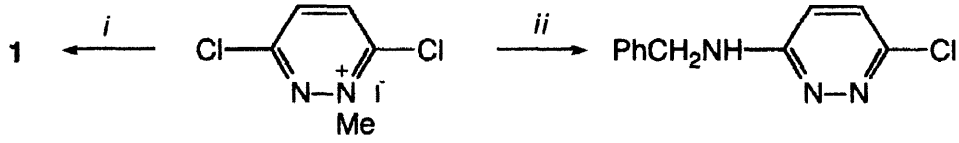
i $Et_3O^+BF_4^-$ in $ClCH_2CH_2Cl$ at room temperature. *ii* **8** → **10**, H_2O at room temperature; **8** → **11**, thiourea in $ClCH_2CH_2Cl$ under reflux, aq. NH_3 at room temperature. *iii* ROH at 50°C. *iv* Et_2NH at 0°C.

Not expectedly, the quaternised pyridazinium salts have an enhanced activity towards nucleophiles. The 3-chloro derivative **8** is converted extremely rapidly into the pyridazinone **10**, while recrystallisation of **8** from methanol, or ethanol, produces the corresponding 3-alkoxypyridazinium salts, **12** and **13**, identical to those obtained by quaternisation of the alkoxypyridazines **3a** and **b**. The pyridazinethione **11** is also obtained under relatively mild conditions *via* the isothiouronium salt.

Reaction of **8** with concentrated ammonia, or phthalimide, followed by hydrazine, produced the pyridazin-3-one **10** in high yield (>80%) and not the 3-amino derivative. This observation contrasts with those seen when **8** reacts with diethylamine to produce the 2-ethyl-3-diethylamino-6-(2-pyrrolyl)pyridazinium salt **14** (>95%), or in the reaction of 3,6-dichloro-1-methylpyridazinium iodide **15** with benzylamine to yield 3-

benzylamino-6-chloropyridazine **16** (90%) *via* nucleophilic attack by the amine at both 3-position and on the N-methyl group. It is probable that, in the reaction of **8** with ammonia under the basic reaction conditions, the imino compound is formed initially but is hydrolysed rapidly to produce the oxo derivative (*cf.* the facile solvolysis of 3-amino-2-methylpyridazinium iodide to give 2-methylpyridazin-3-one under mildly basic conditions[8]).

In view of the reaction **15** with benzylamine it was of interest to examine the reaction of 1-alkyl-3,6-dichloropyridazinium cations with pyrrolylmagnesium bromide. Both **15** and its N-ethyl analogue produced 3-chloro-6-(2-pyrrolyl)pyridazine by nucleophilic displacement of one of the chloro groups and the N-substituent, with no evidence of further nucleophilic attack on the pyridazine ring. Somewhat surprisingly, 3,6-dichloropyridazine-1-oxide was recovered unchanged from its reaction with pyrrolylmagnesium bromide.



15 **16**

i pyrrolylmagnesium bromide in ether at 0°C. *ii* $PhCH_2NH_2$ and Na_2CO_3 at 100°C.

Experimental

Infra-red spectra were recorded on a Perkin-Elmer 297 or 1720X FT-IR spectrometer. JEOL EX90 or JEOL GX 400 spectrometers were used to record ^1H NMR spectra and ^{13}C NMR spectra. Chemical shifts are quoted in ppm down field from Me_4Si.

3-Chloro-6-(2-pyrrolyl)pyridazine (1): 1-Pyrrolylmagnesium bromide [from pyrrole (3.35 g, 50 mmol), and ethyl magnesium bromide (6.6 g, 50 mmol)] in ether (400 ml) was added over 1h to 3,6-dichloropyridazine (7.45 g, 50 mmol) in ether (50 ml). The mixture was stirred at room temperature for 64h and then heated under reflux for 5h. Aqueous ammonium chloride (20%, 35 ml) was added and the mixture was extracted with dichloromethane (2 x 50 ml). The organic extracts were washed with water (3 x 50 ml), dried ($MgSO_4$), and evaporated under reduced pressure. The residual solid was recrystallised from ethanol to give *3-chloro-6-(2-pyrrolyl)pyridazine* (7.0 g, 78%), m.p. 182.4 - 182.7°C (Found: C, 53.5; H, 3.2; N, 23.3 $C_8H_6N_3Cl$ requires C, 53.5; H, 3.4; N, 23.4%). δ_H ($CDCl_3$) 6.24 (1H, dd), 6.94 - 7.02 (2H, m), 7.79 (1H, d), 8.04 (1H, d), 11.95 (1H, bs); δ_C ($CDCl_3$) 109.9 (d), 111.1 (d), 123.0 (d), 125.2 (d), 126.8 (s), 128.7 (d), 152.4 (s), 152.6 (s).

6-(2-Pyrrolyl)-2*H*-pyridazin-3-one (2): (a) 3-Chloro-6-(2-pyrrolyl)pyridazine (0.3 g, 1.6 mmol), and aqueous sodium hydroxide (50%, 20 ml), was refluxed at 100°C for 8h. The mixture was extracted with dichloromethane (50 ml). Evaporation of the dried ($MgSO_4$) extracts only gave starting material (75%), as shown by t.l.c. analysis and melting point.

(b) 3-Chloro-6-(2-pyrrolyl)pyridazine (1.5 g, 9.37 mmol) and aqueous sodium hydroxide (50%, 35 ml) in a bomb calorimeter were heated for 64h at 90°C. The mixture was extracted with ethyl acetate (3 x 50 ml). Evaporation of the dried ($MgSO_4$) extracts yielded the starting material (90%), as shown by t.l.c. analysis.

(c) 3-Chloro-6-(2-pyrrolyl)pyridazine (0.7 g, 3.89 mmol), aqueous sodium hydroxide (50%, 50 ml), and tetra-*n*-butylammonium bromide (3.0 g) in 1,2-dichlorobenzene (50 ml) were heated at 100°C for 2h. The

cooled mixture was filtered and the filtrate was neutralised with aqueous hydrochloric acid (20%) and extracted with ethyl acetate (3 x 50 ml). Hexane was added to the dried ($MgSO_4$) extracts until crystals were produced. from dichloromethane:hexane gave *6-(2-pyrrolyl)-2H-pyridazin-3-one* (0.58 g, 92.3%), m.p. 175.8 - 176.3°C (Found: C, 59.7; H, 4.3; N, 26.1. $C_8H_7N_3O$ requires C, 59.6; H, 4.4; N, 26.1%). δ_H (DMSO-d_6) 6.12 (1H, dd), 6.63 (1H, dd), 6.88 (1H, dd), 6.87 (1H, d), 7.84 (1H, d,), 11.31 (1H, bs), 12.83 (1H, bs); δ_C (DMSO-d_6) 108.8 (d), 109.0 (d), 121.3 (d), 126.9 (s), 130.0 (d), 130.9 (d),139.0 (s), 159.9 (s).

(d) 3-Benzyloxy-6-(2-pyrrolyl)pyridazine (0.36 g, 1.43 mmol) was hydrogenolysed over palladium on charcoal (5%, 0.3 g) in methanol (50 ml) at two atmospheres pressure. On completion of the expected take-up of hydrogen, the solution was filtered and evaporated under reduced pressure to yield **2** (0.20 g, 86.6%), m.p. 175.8 - 176°C.

(e) *n*-Butyllithium (1.6M, 4.0 ml, 6.4 mmol) was added to diphenylphosphine (0.85 ml, 5.0 mmol) in tetrahydrofuran (25 ml) at 0°C and the mixture was allowed to warm to room temperature. 3-Methoxy-6-(2-pyrrolyl)pyridazine (0.66 g, 3.76 mmol) was added and the mixture stirred for 2h. Volatile material was removed under reduced pressure, aqueous sodium bicarbonate (5%, 25 ml) was added, and the mixture was extracted with ethyl acetate (3 x 50 ml). The organic phase was washed with water (50 ml), dried ($MgSO_4$), and evaporated under reduced pressure. Chromatographic purification of the residual solid from silica, using ethyl acetate as the eluant, gave **2** (0.51 g, 84%), m.p. 175.5 - 176.5°C.

General Procedure for the Preparation of 3-Alkoxy-6-(2-pyrrolyl)pyridazines: 3-Chloro-6-(2-pyrrolyl)pyridazine (2.0 g, 11.1 mmol) and the appropriate sodium alkoxide (1.1 mmol) in the corresponding alcohol (20 ml) were refluxed for 72h. The solvent was removed under reduced pressure, water (50 ml) was added and the mixture neutralised with aqueous hydrochloric acid (10%) The mixture was extracted with dichloromethane (100 ml) and the dried ($MgSO_4$) extract was dried and evaporated. Recrystallisation of the residue from ethanol gave the 3-alkoxy-6-(2-pyrrolyl)pyridazine.

3-Methoxy-6-(2-pyrrolyl)pyridazine (**3a**) (90%) had m.p. 174.4 - 174.8°C (Found: C, 61.7; H, 5.1; N, 24.0. $C_9H_9N_3O$ requires C, 61.7; H, 5.2; N, 24.0%). δ_H (DMSO-d_6) 4.04 (3H, s), 6.17 (1H, dd), 6.75 (1H, dd), 6.92 (1H, dd), 7.14 (1H, d), 7.88 (1H, d); δ_C (DMSO-d_6) 54.6 (q), 108.3 (d), 109.0 (d), 118.2 (d), 121.6 (d), 125.0 (d), 126.0 (s), 148.9 (s), 163.4 (s).

3-Ethoxy-6-(2-pyrrolyl)pyridazine (**3b**) (92%) had m.p. 184.6 - 185.3°C (Found: C, 63.5; H, 5.8; N, 22.0. $C_{10}H_{11}N_3O$ requires C, 63.5; H, 5.9; N 22.2%). δ_H (DMSO-d_6) 1.39 (3H, t), 4.50 (2H, q), 6.17 (1H, dd), 6.72 - 6.75 (1H, m), 6.91 (1H, dd), 7.11 (1H, d), 7.86 (1H, d); δ_C (DMSO-d_6) 14.4 (q), 62.3 (t), 108.5 (d), 109.2 (d), 117.6 (d), 121.3 (d), 126.1 (d), 128.4 (s), 149.2 (s), 162.7 (s).

3-Benzyloxy-6-(2-pyrrolyl)pyridazine (**3c**) (98%) had m.p. 210 - 211°C (Found: C, 71.8; H, 5.1; N, 16.8. $C_{15}H_{13}N_3O$ requires C, 71.7; H, 5.2; N, 16.7%). δ_H (DMSO-d_6) 5.58 (2H, s), 6.24 (1H, dd), 6.79 - 7.10 (2H, m), 7.29 (1H, s), 7.40 - 7.65 (5H, m), 8.01 (1H, d); δ_C (DMSO-d_6) 68.0 (t), 108.6 (d), 109.2 (d), 117.8 (d), 121.3 (d), 126.3 (d), 127.9 (d), 128.0 (d), 128.3 (d), 128.8 (s), 136.8 (s), 149.5 (s), 162.6 (s).

3-Hydrazino-6-(2-pyrrolyl)pyridazine (4a): (a) 3-Chloro-6-(2-pyrrolyl)pyridazine (1.5 g, 9.37 mmol) and hydrazine monohydrochloride (1.84 g, 9.37 mmol) in ethanol (100 ml) were refluxed for 8h. Volatile material was removed under reduced pressure, water (100 ml) was added, and the mixture was extracted with ethyl acetate (3 x 50 ml). The dried ($MgSO_4$) extracts were evaporated under reduced pressure. T.l.c. analysis showed the residue to be starting material (90%), as verified by the ^1H NMR.

(b) 3-Chloro-6-(2-pyrrolyl)pyridazine (0.6 g, 3.3 mmol) and hydrazine hydrate (10.0 ml) in *n*-butanol (100 ml) were refluxed for 64h. Volatile material was removed under reduced pressure, water (100 ml) added, and the mixture was extracted with ethyl acetate (3 x 50 ml). The dried ($MgSO_4$) organic extracts were evaporated under reduced pressure and the residual solid was recrystallised from ethanol to yield *3-hydrazino-6-(2-pyrrolyl)pyridazine* (0.53 g, 90%), m.p. 206 - 207°C (Found: C, 55.2; H, 5.0; N, 39.7. $C_8H_9N_5$ requires C, 54.9; H, 5.2; N, 40.0%). δ_H (DMSO-d_6) 4.32 (2H, s), 6.11 (1H, dd), 6.59 (1H, dd), 6.89 (1H, dd), 7.03 (1H, d), 7.66 (1H, d), 11.50 (1H, bs); δ_C (DMSO-d_6) 106.5 (d), 108.7 (d), 113.5 (d), 120.0 (d), 123.8 (d), 129.0 (s), 145.9 (s), 160.5 (s).

3-(2-Phenylhydrazino)-6-(2-pyrrolyl)pyridazine (4b): *n*-Butyllithium in hexane (1.6M, 4.66 ml, 7.46 mmol) was added dropwise over 30 min to 3-chloro-6-(2-pyrrolyl)pyridazine (1.34 g, 7.46 mmol) and phenylhydrazine (0.73 g, 7.46 mmol) in ether (30 ml) at -78°C. The mixture was allowed to come to room temperature and left to stand for 12h before the reaction was quenched with methanol (50 ml). Volatile material was removed under reduced pressure and water (50 ml) was added. The aqueous mixture was extracted with dichloromethane (2 x 50 ml) and the dried ($MgSO_4$) extracts were evaporated to give a product, which was recrystallised from ethanol to yield *3-(2-phenylhydrazino)-6-(2-pyrrolyl)pyridazine* (1.68 g, 90%), m.p. 186 - 186.4°C (Found: C, 67.0; H, 5.2; N, 27.7. $C_{14}H_{13}N_5$ requires C, 66.9; H, 5.2; N, 27.9%). δ_H (DMSO-d_6) 5.42 (2H, bs), 6.20 (1H, dd), 6.72 (1H, dd), 6.88 (1H, dd), 7.10 - 7.69 (5H, m), 7.84 (1H, d), 11.54 (1H, bs); δ_C (DMSO-d_6) 107.3 (d), 109.0 (d), 116.4 (d), 120.6 (d), 122.2 (d), 123.2 (d), 123.7 (d), 128.2 (d), 128.6 (s), 145.9 (s), 146.7 (s), 159.0 (s).

6-(2-Pyrrolyl)-2*H*-pyridazin-3-thione (5): 3-Chloro-6-(2-pyrrolyl)pyridazine (0.39 g, 2.2 mmol) and thiourea (1.0 g, 13.0 mmol) in *n*-butanol (75 ml) were heated at 117°C for 8h. The mixture was concentrated, aqueous ammonia (*d* 0.88, 50 ml) was added, and the mixture was kept at room temperature for 3 days. The mixture was then diluted with water (100 ml) and extracted with ethyl acetate (2 x 50 ml). The dried ($MgSO_4$) extracts were filtered and the solvent was removed under reduced pressure. The residue was recrystallised from benzene to yield *6-(2-pyrrolyl)-2H-pyridazin-3-thione* (0.32 g, 83.2%), m.p. 211 - 212°C (Found: C, 54.2; H, 4.0; N, 23.6. $C_8H_7N_3S$ requires C, 54.2; H, 4.0; N, 23.7%). δ_H (DMSO-d_6) 6.24 (1H, dd), 6.84 - 7.00 (1H, m), 7.00 - 7.18 (1H, m), 7.77 (2H, s); δ_C (DMSO-d_6) 109.6 (d), 110.7 (d), 122.8 (d), 124.0 (d), 125.9 (s), 140.5 (d), 144.3 (s), 155.5 (s).

3-Methylthio-6-(2-pyrrolyl)pyridazine (6): 3-Chloro-6-(2-pyrrolyl)pyridazine (2.0 g, 11.0 mmol) and thiourea (0.84 g, 11.0 mmol) in ethanol (75 ml) were refluxed for 2h. Volatile material was removed under reduced pressure and aqueous sodium hydroxide (20%, 35 ml), benzyltriethylammonium chloride (0.09 g, 0.48 mmol), and methyl iodide (2.91 g, 20.0 mmol) were added to the isothiouronium salt. The mixture was stirred at room temperature for 2h and then heated to 42°C for 2h. The mixture was cooled and filtered. The filtrate was neutralised with hydrochloric acid (20%) and extracted with ethyl acetate (3 x 50 ml). The dried ($MgSO_4$) extracts were evaporated under reduced pressure and the crude product was recrystallised from ethanol:ether to afford *3-methylthio-6-(2-pyrrolyl)pyridazine* (1.5 g, 70.2%), m.p. 164.8 - 165.1°C (Found: C 56.4; H, 4.6; N, 21.75. $C_9H_9N_3S$ requires C, 56.5; H, 4.7; N, 22.0%). δ_H (DMSO-d_6) 2.71 (3H, s), 6.26 (1H, dd), 6.90 - 7.03 (2H, m), 7.60 (1H, d), 7.82 (1H, d), 11.83 (1H, bs); δ_C (DMSO-d_6) 12.6 (q), 109.4 (d), 110.0 (d), 121.8 (d), 121.9 (d), 125.6 (d), 127.7 (s), 149.9 (s), 158.7 (s).

3-(2-Pyrrolyl)pyridazine (7): 3-Chloro-6-(2-pyrrolyl)pyridazine (1.52 g, 8.5 mmol), ammonium formate (2.6 g, 43.0 mmol), and 10% palladium/carbon (0.38 g) in methanol (50 ml) were stirred at room temperature

under nitrogen. The reaction was monitored by t.l.c. and, when complete, the reaction mixture was filtered and the volatiles were removed under reduced pressure. Water (100 ml) was added and the mixture was extracted with ethyl acetate (50 ml). The dried ($MgSO_4$) extract was evaporated under reduced pressure and the product was crystallised from ethyl acetate to give *3-(2-pyrrolyl)pyridazine* (1.1 g, 89.3%) m.p. 154.6 - 155.0°C (Found: C, 66.15; H, 4.9; N, 28.9. $C_8H_7N_3$ requires C, 66.2; H, 4.9; N, 28.95%). δ_H (DMSO-d_H) 6.23 (1H, dd), 6.85 - 7.10 (2H, m), 7.60 (1H, dd), 7.98 (1H, dd), 9.02 (1H, dd), 11.50 (1H, bs); δ_C (DMSO-d_6) 109.6 (d), 109.8 (d), 121.7 (d), 122.1 (d), 127.0 (d), 128.0 (s), 148.7 (d), 152.8 (s).

Attempted Preparation of 3-Amino-6-(2-pyrrolyl)pyridazines: (a) 3-Chloro-6-(2-pyrrolyl)-pyridazine (1.5 g, 9.37 mmol) and aqueous ammonia (10%, 50 ml) were refluxed for 8h. The aqueous mixture was neutralised with dilute hydrochloric acid (10%), extracted with ethyl acetate (3 x 50 ml), and the dried ($MgSO_4$) extracts were evaporated under reduced pressure. T.l.c. analysis showed the mixture to be starting material (90%), as verified by the ^1H NMR.

(b) Nickel-aluminium alloy (0.3 g) was progressively added in small quantities to 3-hydrazino-6-(2-pyrrolyl)-pyridazine (1.35 mmol) in ethanol (11.7 ml) and aqueous potassium hydroxide (1M, 11.7 ml). The mixture was stirred for 2h, filtered through neutral silica, and evaporated under reduced pressure. Water (50 ml) was added and the mixture was extracted with ethyl acetate (3 x 50 ml). The dried ($MgSO_4$) extracts were evaporated under reduced pressure. T.l.c. analysis and ^1H NMR spectral data indicated that the product it to be starting material (>90%).

A similar reaction with the phenylhydrazino derivative also failed to give the aminopyridazine.

(c) Potassium phthalimide (23.34 g, 0.126 mol) was added with cooling to 3-chloro-6-(2-pyrrolyl)pyridazine (0.75 g, 4.1 mmol) in dimethylformamide (20 ml). The mixture was heated at 70°C for 36h, cooled to room temperature, and the solvent was evaporated under reduced pressure. Hydrazine hydrate (3 ml) in methanol (50 ml) was added and the mixture was refluxed for 5h. Volatile material was removed under reduced pressure, water (50 ml) was added, and the mixture was extracted with ethyl acetate (3 x 50 ml). The dried ($MgSO_4$) extracts were evaporated and t.l.c. analysis showed the residue to be starting material (>90%).

(d) 3-Chloro-6-(2-pyrrolyl)pyridazine (2.32 g, 12.7 mmol), *n*-butylamine (20 ml, 0.19 mol) and potassium carbonate (5.0 g) were heated in DMSO (50 ml) at 80°C for 8h. Volatile material was removed under reduced pressure and water (50 ml) was added. The mixture was extracted with dichloromethane (2 x 50 ml), dried ($MgSO_4$) extracts were evaporated under reduced pressure to yield starting material (89%), as shown by the melting point and ^1H NMR spectroscopy.

(e) *n*-Butyllithium in hexane (1.6 M, 1.15 ml, 3.4 mmol) was added dropwise to *n*-butylamine (0.34 ml, 3.4 mmol) in ether (10 ml) at -78°C and the solution was added dropwise to 3-chloro-6-(2-pyrrolyl)pyridazine (0.31 g, 1.7 mmol) in ether (50 ml). The mixture was stirred for 1h at -78°C, warmed to room temperature, and left to stand for 12h. The reaction was quenched with methanol (50 ml), the volatiles were removed under reduced pressure, and water (50 ml) was added. The aqueous mixture was extracted with dichloromethane (2 x 50 ml) and the dried ($MgSO_4$) extracts were evaporated to yield starting material (78%), as shown by the melting point and ^1H NMR spectroscopy.

3-Chloro-2-ethyl-6-(2-pyrrolyl)pyridazinium tetrafluoroborate (8): Triethyloxonium tetrafluoroborate (1.0 g, 5.7 mmol) and 3-chloro-6-(2-pyrrolyl)pyridazine (1.0 g, 5.5 mmol) in 1,2-dichloroethane (80 ml) were stirred for 2h. Solvent was removed under reduced pressure and the residue was recrystallised from dichloromethane:hexane to yield *3-chloro-2-ethyl-6-(2-pyrrolyl)pyridazinium tetrafluoroborate*, (1.57 g, 95%),

m.p. 160.6 - 161.0°C (Found: C, 40.65; H, 3.7; N, 14.2. $C_{10}H_{11}N_3ClBF_4$ requires C, 40.65; H, 3.7; N, 14.0%). δ_H (DMSO-d_6) 1.68 (3H, t), 4.85 (2H, q), 6.42 (1H, dd), 7.34 - 7.38 (2H, m), 8.64 (1H, d), 8.76 (1H, d); δ_C (DMSO-d_6) 13.7 (q), 59.1 (t), 111.9 (d), 116.6 (d), 124.1 (d), 127.3 (s), 132.7 (d), 137.2 (d), 149.4 (s), 153.0 (s).

1-Ethyl-3-(2-pyrrolyl)pyridazinium tetrafluoroborate (9): Triethyloxonium tetrafluoroborate (1.0 g, 5.7 mmol) and 3-(2-pyrrolyl)pyridazine (1.0 g, 6.4 mmol) in 1,2-dichloroethane (50 ml) were stirred for 2h. The solvent was removed under reduced pressure and the residue was recrystallised from ethanol to give *1-ethyl-3-(2-pyrrolyl)pyridazinium tetrafluoroborate* (1.73 g, 96%), m.p. 159.6 - 160.0°C (Found: C, 45.9; H, 4.5; N, 16.0 $C_{10}H_{12}N_3BF_4$ requires C, 46.0; H, 4.6; N, 16.15%). δ_H (DMSO-d_6) 1.65 (3H, t), 4.73 (2H, q), 6.39 (1H, dd), 7.20 - 7.38 (2H, m), 8.50 (1H, dd), 8.84 (1H, d), 9.52 (1H, d); δ_C (DMSO-d_6) 14.4 (q), 60.1 (t), 111.3 (d), 115.6 (d), 124.4 (s), 126.4 (d), 130.9 (d), 134.7 (d), 145.2 (d), 154.6 (s).

3-Alkoxy-2-ethyl-6-(2-pyrrolyl)pyridazinium tetrafluoroborates: (a) A mixture of triethyloxonium tetrafluoroborate (0.7 g, 3.7 mmol) and the appropriate 3-alkoxy-6-(2-pyrrolyl)pyridazine (3.7 mmol) was stirred at room temperature in 1,2-dichloroethane (40 ml) for 2h. The precipitated solid was collected and recrystallised from the appropriate alcohol to yield the appropriate 3-alkoxy-2-ethyl-6-(2-pyrrolyl)pyridazinium tetrafluoroborate.

(b) 3-Chloro-2-ethyl-6-(2-pyrrolyl)pyridazinium tetrafluoroborate (1.0 g, 3.38 mmol) was heated to 50°C in the appropriate alcohol (10 ml) for 10 min. Volatile material was removed under reduced pressure and the residue was recrystallised from the appropriate alcohol to afford the corresponding 3-alkoxy-2-ethyl-6-(2-pyrrolyl)pyridazinium tetrafluoroborate.

2-Ethyl-3-methoxy-6-(2-pyrrolyl)pyridazinium tetrafluoroborate **(12)** (Method a: 97.5%; Method b: 90%) had m.p. 175.7 - 176.2°C (Found: C, 45.45; H, 4.7; N, 14.2. $C_{11}H_{14}N_3OBF_4$ requires C, 45.4; H, 4.85; N, 14.4%). δ_H (DMSO-d_6) 1.56 (3H, t), 4.41 (3H, s), 4.44 (2H, q), 6.35 (1H, dd), 7.21 (2H, t), 8.35 (1H, d), 8.81 (1H, d); δ_C (DMSO-d_6) 12.6 (q), 52.0 (d), 60.0 (t), 110.6 (d), 113.7 (d), 122.4 (d), 124.4 (s), 124.9 (d), 134.6 (d), 147.8 (s), 160.4 (s).

3-Ethoxy-2-ethyl-6-(2-pyrrolyl)pyridazinium tetrafluoroborate **(13)** (Method a: 98%; Method b: 96%) had m.p. 188.3 - 188.6°C (Found: C, 47.45; H, 5.15; N, 13.6. $C_{12}H_{16}N_3OBF_4$ requires C, 47.2; H, 5.3; N, 13.8%). δ_H (DMSO-d_6) 1.42 (6H, t), 4.45 (2H, q), 4.71 (2H, q), 6.34 (1H, dd), 7.14 - 7.30 (2H, m), 8.27 (1H, d), 8.73 (1H, d); δ_C (DMSO-d_6) 12.6 (q), 14.0 (q), 52.1 (t), 69.9 (t), 110.6 (d), 113.6 (d), 122.6 (d), 124.4 (s), 124.9 (d), 134.6 (d), 147.7 (s), 159.6 (s).

2-Ethyl-6-(2-pyrrolyl)pyridazin-3-one (10): (a) 3-Chloro-2-ethyl-6-(2-pyrrolyl)pyridazinium tetrafluoroborate (1.0 g, 3.38 mmol) in water (50 ml) was stirred at room temperature for 16h. The solution was concentrated under reduced pressure and the precipitated solid was recrystallised from dichloromethane:hexane to yield *2-ethyl-6-(2-pyrrolyl)pyridazin-3-one* (1.6 g, 96%) m.p. 111.8-112.1°C (Found: C, 63.8; H, 5.8; N, 22.0. $C_{10}H_{11}N_3O$ requires C, 63.5; H, 5.9; N, 22.2%). δ_H (DMSO-d_6) 1.32 (3H, t), 4.11 (2H, q), 6.17 (1H, dd), 6.60 - 6.70 (1H, m), 6.88 - 6.98 (1H, m), 6.94 (1H, d), 7.81 (1H, d), 11.32 (1H, bs); δ_C (DMSO-d_6) 13.3 (q), 45.8 (t), 108.9 (d), 109.1 (d), 121.4 (d), 126.7 (s), 129.5 (d), 129.9 (d), 138.8 (s), 158.2 (s).

(b) 3-Chloro-2-ethyl-6-(2-pyrrolyl)pyridazinium tetrafluoroborate (0.58 g, 1.96 mmol) in aqueous ammonia (20%, 50 ml) was refluxed for 1h. The mixture was diluted with water (50 ml) and the aqueous solution was continuously extracted with dichloromethane. The dried ($MgSO_4$) extracts were concentrated under reduced

pressure and the residue was recrystallised from dichloromethane:hexane to yield **10** (0.33 g, 87.7%), m.p. 111.8 - 112.1.

(c) Potassium phthalimide (0.55 g, 3.0 mmol) was added to 3-chloro-2-ethyl-6-(2-pyrrolyl)pyridazinium tetrafluoroborate (0.76 g, 2.57 mmol) in dimethylformamide (20 ml) at 0°C. The mixture was heated at 70°C for 30 min, cooled, and the solvent was then evaporated under reduced pressure. Hydrazine hydrate (3.0 ml) in methanol (50 ml) was added and the mixture was refluxed for 2h. Volatile material was removed under reduced pressure and water (25 ml) was added. The mixture was extracted with dichloromethane (2 x 50 ml), the organic extracts were washed with water (3 x 50 ml), dried ($MgSO_4$), and evaporated under reduced pressure to yield **10** (0.40 g, 82.2%), m.p. 111.6 - 112°C.

2-Ethyl-6-(2-pyrrolyl)pyridazin-3-thione (11): 3-Chloro-2-ethyl-6-(2-pyrrolyl)pyridazinium tetrafluoroborate (1.33 g, 5.1 mmol) and thiourea (0.39 g, 5.1 mmol) in dichloromethane (75 ml) were refluxed for 3h, and then mixed with aqueous ammonia (d 0.88, 50 ml). The mixture was kept at room temperature for 3 days and then evaporated under reduced pressure to yield the crude product, which was recrystallised from dichloromethane:hexane to give *2-ethyl-6-(2-pyrrolyl)pyridazin-3-thione* (1.40 g, 92.3%), m.p. 125.1 - 125.6°C (Found: C, 58.7 H, 5.2; N, 20.5. $C_{10}H_{11}N_3S$ requires C, 58.5; H, 5.4; N, 20.5%). δ_H ($CDCl_3$) 1.48 (3H, t), 4.75 (2H, q), 6.27 (1H, dd), 6.80 - 6.85 (1H, m), 6.85 - 7.05 (1H, m), 7.18 (1H, d), 7.75 (1H, d); δ_C (DMSO-d_6) 12.5 (q), 49.6 (t), 109.7 (d), 110.9 (d), 122.9 (d), 125.6 (s), 126.6 (d), 129.4 (d), 142.4 (s), 157.9 (s).

3-Diethylamino-2-ethyl-6-(2-pyrrolyl)pyridazinium tetrafluoroborate (14): Diethylamine (50.0 ml) was added to 3-chloro-2-ethyl-6-(2-pyrrolyl)pyridazinium tetrafluoroborate (1.62 g, 5.5 mmol) at 0°C and then heated at 50°C for 1h. Volatile material was removed under reduced pressure and the residue was recrystallised from dichloromethane:hexane to yield *3-diethylamino-2-ethyl-6-(2-pyrrolyl)pyridazinium tetrafluoroborate* (1.76g, 96.7%), m.p. 161.7 - 162.2°C (Found: C, 50.75; H, 6.2; N, 16.8 $C_{14}H_{21}N_4BF_4$ requires C, 50.6; H, 6.4; N, 16.9%). δ_H (DMSO-d_6) 1.24 (6H, t), 1.59 (3H, t), 3.59 (4H, q), 4.38 (2H, q), 6.30 (1H, dd), 7.06 - 7.26 (2H, m), 8.09 (1H, d), 8.38 (1H, d); δ_C (DMSO-d_6) 12.6 (q), 13.6 (q), 45.8 (t), 54.4 (t), 110.3 (d), 113.0 (d), 124.4 (d), 124.8 (s), 128.2 (d), 129.6 (d), 146.4 (s), 156.9 (s).

3,6-Dichloro-1-ethylpyridazinium tetrafluoroborate: A mixture of triethyloxonium tetrafluoroborate (1.0 g, 5.7 mmol) and 3,6-dichloropyridazine (0.85 g, 5.7 mmol) in 1,2-dichloroethane (40 ml) was stirred for 2h. The precipitated salt was collected and recrystallised from dichloromethane:ether to give *3,6-dichloro-1-ethylpyridazinium tetrafluoroborate* (1.46 g, 97.0%), m.p. 102.1 - 102.4°C (Found: C, 27.3; H, 2.5; N, 10.3 $C_6H_7N_2Cl_2BF_4$ requires C, 27.2; H, 2.7; N, 10.6%). δ_H (DMSO-d_6) 1.32 (3H, t), 4.09 (2H, q), 7.03 (1H, d), 7.52 (1H, d); δ_C (DMSO-d_6) 13.5 (q), 46.6 (t), 132.3 (d), 134.2 (d), 137.0 (s), 158.5 (s).

3-Chloro-1-ethylpyridazin-6-one: 3,6-Dichloro-1-ethylpyridazinium tetrafluoroborate (0.62 g, 2.3 mmol) in water (30 ml) was stirred at room temperature for 16h. The solution was concentrated under reduced pressure and the residue was distilled b.p. 125°C at 1mm Hg to yield *3-chloro-1-ethylpyridazin-6-one* (0.34 g, 92%) (Found: C, 45.3; H, 4.3; N, 17.6 $C_6H_7N_2OCl$ requires C, 45.5; H, 4.45; N, 17.7%). δ_H (DMSO-d_6) 1.30 (3H, t), 4.08 (2H, q), 7.04 (1H, d), 7.56 (1H, d); δ_C (DMSO-d_6) 13.2 (q), 46.3 (t), 132.1 (d), 133.9 (d), 136.6 (s), 158.1 (s).

3-Benzylamino-6-chloropyridazine (16): 3,6-Dichloro-1-methylpyridazinium iodide (m.p. 115.5 - 116°C, prepared from 3,6-dichloropyridazine and iodomethane, *cf.* ref. 9) (2.1 g, 7.2 mmol), benzylamine (30.0 g, 0.27 mol), and sodium carbonate (1.0 g) were heated at 100°C for 8h. The volatiles were removed

under reduced pressure and water (100 ml) was added. The solid was collected, dried and recrystallised from ethanol:ether to give 3-benzylamino-6-chloropyridazine (2.76 g, 90%), m.p. 161.3 - 162.0°C (lit.,[8] m.p. 163 - 164°C). δ_H (DMSO-d_6) 4.09 (2H, s), 7.13 (1H, d), 7.47 - 7.65 (6H, m), 8.76 (1H, bs).

Reaction of Pyrrolylmagnesium Bromide with 1-Alkyl-3,6-dichloropyridazinium Cations: (a) 3,6-Dichloro-1-ethylpyridazinium tetrafluoroborate (2.0 g, 7.5 mmol) in ether (50 ml) was added to 1-pyrrolylmagnesium bromide [from pyrrole (1.0 g, 15 mmol), and ethylmagnesium bromide (2.0 g, 15 mmol)] in ether (40 ml) over 1h.. After 64h at room temperature, the mixture was heated under reflux for 5h. Aqueous ammonium chloride (20%, 35 ml) was added to the mixture, which was then extracted with dichloromethane (2 x 50 ml). The organic extracts were washed with water (3 x 50 ml), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was recrystallised from ethanol to give **1** (1.22 g, 90%), m.p. 182.5 - 182.5°C. (b) 1-Pyrrolylmagnesium bromide [from pyrrole (3.35 g, 50 mmol), and ethylmagnesium bromide (6.6 g, 50 mmol)] in ether (400 ml) was added portionwise over 1h to 3,6-dichloro-1-methylpyridazinium iodide[9] (7.0 g, 50 mmol) in ether (50 ml).The mixture was stirred at room temperature for 64h and then heated under reflux for 5h. Aqueous ammonium chloride (20%, 35 ml) was added to the mixture and the aqueous mixture was extracted with dichloromethane (2 x 50 ml). The organic extracts were washed with water (3 x 50 ml), dried ($MgSO_4$), and evaporated to yield a crude product, which was recrystallised from ethanol to give **1** (5.0 g, 56.4%), m.p. 182.0 - 182.5°C.

Reaction of Pyrrolylmagnesium Bromide with 3,6-Dichloropyridazine-1-oxide: 1-Pyrrolylmagnesium bromide [from pyrrole (3.35 g, 50.0 mmol), and ethyl magnesium bromide (6.6 g, 50 mmol)] in ether (400 ml) was added over 1h to 3,6-dichloropyridazine-1-oxide[10] (7.05 g, 50.0 mmol) in ether (50 ml). After 64h at room temperature the mixture was heated under reflux for 5h. Aqueous ammonium chloride (20%, 35 ml) was added to the mixture, which was then extracted with dichloromethane (2 x 50 ml). The organic extracts were washed with water (3 x 50 ml), dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The residual solid was recrystallised from ethanol and was shown by t.l.c. analysis and ^1H NMR spectroscopy to be essentially (86%) the unchanged pyridazine-1-oxide.

REFERENCES

1. Jones, R.A.; Karatza, M.; Voro, T.N.; Civcir, P.U.; Franck, A.; Öztürk, O.; Seaman, J.P.; Whitmore A.P.; Williamson, D.J. *Tetrahedron,* **1996**, *52*, 8707 - 8724.
2. Jones, R.A.; Civcir, P.U. *Tetrahedron*, **1997**, *53*, 11529 - 11540
3. Öztürk, O. MSc Dissertation, University of East Anglia, **1995**
4. Hinz, W.; Jones, R.A.; Patel, S.U.; Karatza, M. *Tetrahedron*, **1986**, *42*, 3753 - 3758.
5. Tisler, M.; Stanovnik, B. in *Comprehensive Heterocyclic Chemistry*; Vol. 3, Boulton, A.J.; McKillop, A., Eds; Pergamon: Oxford, **1984**, 1 - 56; Coates, W.J. in *Comprehensive Heterocyclic Chemistry II*, Vol. 6, Boulton, A.J., Ed; Pergamon: Oxford, **1996**, 1 - 92.
6. Coates, W.J.; McKillop, A. *J. Org. Chem.*, **1990**, *55*, 5418 - 3420.
7. Jones, R.A.; Powell, A.K.; Whitmore, A.P. *Acta Cryst.*, **1996**, *C52*, 1002 - 1003.
8 Barlin, G.B. *J. Chem. Soc., Perkin Trans. 1*, **1976**, 1424 - 1429.
9. Lund, H.; Lunde, P. *Acta Chem. Scand.*, **1967**, *21*, 1067 - 1080.
10. Pollak, A.; Zupan, M.; Sket, B. *Synthesis*, **1973**, 495 - 496.