PYRIDAZINES XXVII[1]. ACYLATION REACTIONS AND PROCEDURES FOR REGIOSELECTIVE ALKYLATION OF (5-AMINO-4-PYRIDAZINYL)-ARYLKETONES

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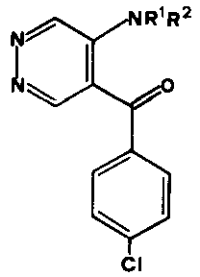
Abstract — Various amides 2a-d,3,4 derived from (5-amino-4-pyridazinyl)-arylketones were prepared. Amino ketone 1 was found to be attacked by alkyl halides exclusively at N-2 yielding iminium salts 9a,9b, whereas reaction of tosylamide 3 with methyl iodide/sodium hydride gave a mixture of two isomeric methylation products (5,8). However, condensation of 1 with ortho esters, followed by sodium borohydride reduction of the intermediate ethyl imidates 12a-c and subsequent oxidation provides a convenient procedure for the preparation of (5-alkylamino-4-pyridazinyl)-arylketones 7a-c.

Recently, we reported the preparation of a novel class of heteroaromatic analogs of 2-aminobenzophenone, namely (5-amino-4-pyridazinyl)-arylketones.[2] In the course of a program directed to the synthesis of potentially bio-active compounds we now became interested in acylation as well as alkylation products of these amino ketones. In order to provide most simple signal patterns in the aromatic proton region of ^{1}H-NMR spectra, the investigations described in this paper were carried out employing (5-amino-4-pyridazinyl)-(4-chlorophenyl)methanone 1.[2]

Acetylation and formylation of 1 were easily accomplished by treating the amino ketone with an excess of acetic anhydride or acetic formic anhydride,[3] respectively. Moreover, as shown from experiments with acetic acid, benzyloxycarbonylglycine, and phthaloylglycine, acylation of 1 can be achieved also under very mild reaction conditions by application of the dicyclohexylcarbodiimide (DCC) method.[4] However, the amide bonds in compounds 2a,2c,2d were found to be cleaved with remarkable ease[5] due to the electron-withdrawing effect of the carbonyl-conjugated pyridazine nucleus. In contrast, the 4-toluenesulfonamide 3, prepared by heating 1 with tosyl chloride/pyridine, proved to be stable under acidic as well as alkaline conditions.



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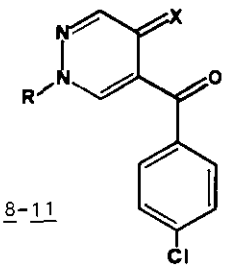

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	R^1	R^2
1	H	H
2a	CH_3CO	H
2b	HCO	H
2c	Z-$NHCH_2CO$	H
2d	Pht-NCH_2CO	H
3	$CH_3C_6H_4SO_2$	H
4	C_2H_5OCO	H
5	$CH_3C_6H_4SO_2$	CH_3
6	CH_3CO	CH_3
7a	H	CH_3
7b	H	C_2H_5
7c	H	n-C_3H_7

	R	X
8	CH_3	$NSO_2C_6H_4CH_3$
9a	CH_3	$NH_2^+I^-$
9b	$C_6H_5CH_2$	$NH_2^+Br^-$
10a	CH_3	O
10b	$C_6H_5CH_2$	O
11	H	O

Tosylamide 3 on treatment with methyl iodide/sodium hydride in DMF solution yielded two isomeric methylated products which could be separated by medium pressure liquid chromatography. The structure of the main component 8 (73% yield) follows unambiguously from analytical and spectroscopic data of the dioxo compound 10a obtained on treatment of 8 with 65% sulfuric acid at 90°C. On the other hand, there is no doubt about the structure of 10a as this compound also results from 9a (see below). Thus, the second methylation product (17% yield) has to be formulated as N-methyltosylamide 5, since other isomeric structures to be taken into consideration would not be in accordance with the IR data obtained ($\nu_{C=O}$ at 1680 cm^{-1}).

Like tosylamide 3, the urethane 4, available in high yield by refluxing 5-(4-chlorobenzoyl)-4-pyridazinecarboxylic acid azide[2] in absolute ethanol, was found to be attacked by methyl iodide under similar reaction conditions at the ring-N-2 atom rather than at the exocyclic nitrogen atom as shown by the ^{1}H-NMR spectrum of the mixture obtained after alkaline work-up.

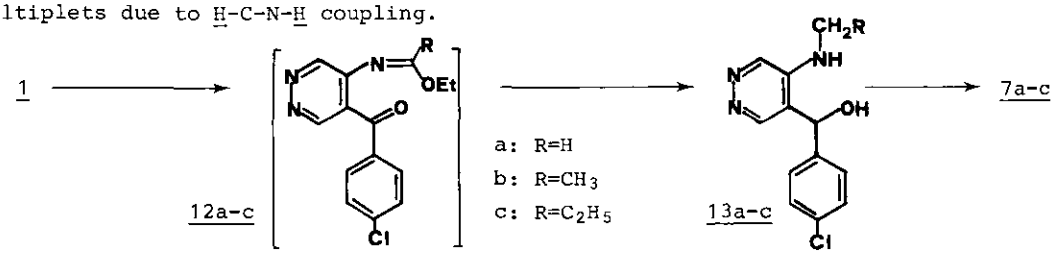
Introduction of alkyl groups (e.g. methyl, benzyl) exclusively at N-2 could be achieved simply by treating 1 with the appropriate alkyl halides in acetone solution.[6] The structure proof of the resulting iminium salts 9a,9b rests on elemental analyses, IR and ^{1}H-NMR data ($\nu_{C=O}$ at 1635 cm^{-1} or 1640 cm^{-1}, respectively;

appearance of the CH_3- and the CH_2-signals as singlets in the NMR spectra of d_6-DMSO solutions). Accordingly, hydrolysis of these compounds afforded N-alkylated 4-pyridazinones 10a,10b. The IR spectrum of 1-benzyl-5-(4-chlorobenzoyl)-4(1H)-pyridazinone (10b) exhibits two $\nu_{C=O}$ signals (1640, 1630 cm^{-1}), whereas in the case of the methyl analog 10a (shown to be identical with the product obtained by acidic hydrolysis of 8 mentioned above) the $\nu_{C=O}$ vibration bands overlap (1650-1645 cm^{-1}). Furthermore, the proposed structures of compounds 9a,9b are supported by the ease of their conversion into pyrazolo[3,4-d]pyridazine derivatives.[7]

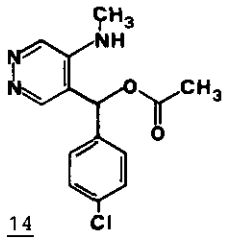
Removal of the benzyl group from 10b applying a procedure reported by Oda[8] permits an access to so far unknown 5-aroyl-4(1H)-pyridazinones like 11.

Methylation of the exocyclic nitrogen atom does take place if the amino ketone 1 is subjected to reaction with dimethyl sulfate/sodium hydroxide under phase-transfer conditions, as shown by appearance of the methyl signal as a doublet in the ^{1}H-NMR spectrum of resulting 7a; however this procedure, successfully employed for the preparation of 2-methylaminobenzophenones,[9] gives only moderate yields of the desired diaza analog.

These findings prompted us to investigate reduction reactions of appropriate precursors like amides or imido esters derived from 1. Whereas reduction of 3-formylamino-pyridine to 3-methylaminopyridine with borane-methyl sulfide was reported to take place in about 90% yield,[3] only minor amounts of the expected methylamino alcohol 13a could be isolated when 2b was subjected to this procedure.[10] However, Crochet and Blanton's method of monoalkylation of heteroaromatic amines[11] was found to provide a convenient route to so far not accessible (5-alkylamino-4-pyridazinyl)-aryl-ketones. Thus, the secondary amines 7a-c were prepared in 55-73% overall yield by condensation of 1 with the appropriate ortho ester followed by sodium borohydride reduction of the intermediate alkyl imidates 12a-c[12] (not isolated) and subsequent potassium permanganate oxidation of the resulting alkylamino alcohols 13a-c. As expected, in the ^{1}H-NMR spectra of these N-alkylamino compounds the signals of the CH_3- or of the CH_2-groups, respectively, adjacent to the nitrogen atom appear as multiplets due to H-C-N-H coupling.



In contrast to the reaction behavior observed with 1, (5-alkylamino-4-pyridazinyl)-arylketones withstand acylation if the DCC method is employed as shown by attempted conversion of 7a into its N-acetyl derivative. Tertiary amide 6, however, could be prepared by refluxing 7a in acetic anhydride. Attempts to prepare 6 under less drastical reaction conditions by DCC acetylation of alcohol 13a and subsequent permanganate oxidation failed in spite of the fact that the reactivity of the amino function in this case should be enhanced due to the lack of conjugation with a carbonyl group. ^{1}H-NMR and IR spectra of the product obtained after treatment of 13a with acetic acid/DCC unequivocally show the new compound to be the ester 14 and not the desired tertiary amide.



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In summary, the present investigations give rise to convenient procedures for the preparation of N-2-alkylated as well as amino-alkylated pyridazine analogs of 2-aminobenzophenone.

EXPERIMENTAL

Melting points (uncorrected): Kofler hot-stage microscope; IR spectra: Jasco IRA-1 spectrometer (KBr disks); ^{1}H-NMR spectra: Varian EM 390 spectrometer (90 MHz; chemical shifts in ppm downfield from internal TMS); column chromatography: Kieselgel 60 (0.063-0.200 mm, Merck); medium pressure liquid chromatography (MPLC): Lobar^R prepacked columns (LiChroprep Si 60, 0.040-0.063 mm, Merck), detection at 280 nm. Microanalyses were performed at the "Institut für Physikalische Chemie" (University of Vienna, Dr.Zak).

N-[5-(4-Chlorobenzoyl)-4-pyridazinyl]acetamide (2a)

a) A solution of 1 (233 mg, 1 mmol) in acetic anhydride (15 ml) was heated to 80°C for 1 h. Most of the reagent was distilled off under reduced pressure, the residue was poured into ice-water, and extracted with CH_2Cl_2. The extract was washed with water, dried, and the solvent was evaporated. Recrystallisation from butanone-diisopropyl ether yielded 215 mg (78%) of colourless needles, mp 146-149°C. IR: 1710, 1680 cm^{-1}; NMR(δ,d_6-DMSO): 1.95(s,3H,CH_3),7.55-7.85(AA'BB',J≈9Hz,4H,C_6H_4Cl),9.05, 9.40(s,1H each,pyridazine-H); Anal.calcd.for $C_{13}H_{10}ClN_3O_2$: C,56.64; H,3.66; N,15.24; Cl,12.86. Found: C,56.75; H,3.83; N,15.34; Cl,12.68.

b) To a solution of 1 (233 mg, 1 mmol) and acetic acid (120 mg, 2 mmol) in THF (25 ml) was added DCC (268 mg, 1.3 mmol), and the mixture was stirred at room temperature for 10 h. Dicyclohexylurea (DCU) was filtered off and the filtrate was

evaporated. Recrystallisation of the residue gave 234 mg (85%) of pure 2a.

N-[5-(4-Chlorobenzoyl)-4-pyridazinyl]formamide (2b)

To a solution of acetic formic anhydride freshly prepared[3] from 98% formic acid (3.75 g, 80 mmol) and acetic anhydride (6.75 g, 65 mmol) in THF (5 ml) was added 1 (233 mg, 1 mmol), and the mixture was stirred at room temperature for 1 h. After evaporation, recrystallisation of the residue from butanone afforded 190 mg (72%) of colourless crystals, mp 174-176°C. IR: 1710,1670 cm^{-1}; NMR(δ,d_6-DMSO): 7.60-7.90(AA'BB',J≈9Hz,4H,C_6H_4Cl),8.40(s,1H,HCO),9.10,9.75(s,1H each,pyridazine-H),10.9 (broad,1H,NH); Anal.calcd.for $C_{12}H_8ClN_3O_2$: C,55.08; H,3.08; N,16.06; Cl,13.55. Found: C,55.06; H,3.23; N,15.87; Cl,13.98.

N-[5-(4-Chlorobenzoyl)-4-pyridazinyl]-N'-benzyloxycarbonylglycine Amide (2c)

A solution of 1 (233 mg, 1 mmol), benzyloxycarbonylglycine (230 mg, 1.1 mmol), and DCC (248 mg, 1.2 mmol) in THF (25 ml) was stirred at room temperature for 10 h. DCU was filtered off and the filtrate was evaporated. Recrystallisation from benzene gave 348 mg (82%) of colourless crystals, mp 115-116°C. IR: 1720,1700,1670 cm^{-1}; NMR(δ,d_6-DMSO): 3.75(d,J=7Hz,s after D_2O addition,2H,NCH_2),5.00(s,2H,OCH_2),7.35 (s,5H,C_6H_5),7.55-7.85(AA'BB',J≈9Hz,C_6H_4Cl,overlapped by a broad signal of NH,5H), 9.10,9.60(s,1H each,pyridazine-H),10.90(broad,1H,NH); Anal.calcd.for $C_{21}H_{17}ClN_4O_4$: C,59.37; H,4.03; N,13.19; Cl,8.34. Found: C,59.70; H,4.10; N,12.94; Cl,8.83.

N-[5-(4-Chlorobenzoyl)-4-pyridazinyl]phthaloylglycine Amide (2d)

Preparation as described for 2c from 1 and phthaloylglycine. Recrystallisation from methanol gave 341 mg (81%) of pale yellow needles, mp 205-209°C. IR: 1770,1720, 1640 cm^{-1}; NMR(δ,d_6-DMSO): 4.30(s,2H,CH_2),7.50-7.80(AA'BB',J≈9Hz,4H,C_6H_4Cl),7.90 (s,4H,phthaloyl-H),9.10,9.50(s,1H each,pyridazine-H),11.10(broad,1H,NH); Anal.calcd. for $C_{21}H_{13}ClN_4O_4$: C,59.94; H,3.11; N,13.31; Cl,8.42. Found: C,60.04; H,3.27; N,13.28; Cl,8.61.

N-[5-(4-Chlorobenzoyl)-4-pyridazinyl]-4-toluenesulfonamide (3)

A solution of 1 (233 mg, 1 mmol) and 4-toluenesulfonyl chloride (285 mg, 1.5 mmol) in pyridine (15 ml) was stirred at 120°C for 3 h. After evaporation, the residue was dissolved in 1N NaOH (30 ml). The solution was treated with charcoal, filtered, and adjusted to pH 3 by addition of 6N HCl. The precipitate (260 mg, 67%) was recrystallized from methanol affording pale yellow crystals, mp 240-242°C. IR: 1660 cm^{-1}; NMR(δ,d_6-DMSO): 2.35(s,3H,CH_3),7.15-7.80(two overlapping AA'BB' patterns,

J≈9Hz and 10Hz,respectively,8H,phenyl-H),8.80,9.10(s,1H each,pyridazine-H); Anal. calcd.for $C_{18}H_{14}ClN_3O_3S$: C,55.74; H,3.64; N,10.83. Found: C,55.55; H,3.81; N,10.71.

Methylation of 3

To a stirred solution of 3 (388 mg, 1 mmol) in dry DMF (20 ml) sodium hydride (30 mg of a 80% suspension in liquid paraffin, 1 mmol) was added and the mixture was cooled to 0°C. A solution of methyl iodide (170 mg, 1.2 mmol) in dry DMF (1 ml) was added dropwise, stirring was continued at 0°C for 0.5 h and then at room temperature for 2 h. After removal of the solvent under reduced pressure, the residue was treated with water and extracted with CH_2Cl_2. Evaporation of the extract gave a mixture of 5 and 8, which was separated by MPLC (column size B, eluent: CH_2Cl_2-ethyl acetate, 2+1). The first fractions gave 295 mg (73%) of N-[5-(4-chlorobenzoyl)-1-methyl-4(1H)-pyridazinylidene]-4-toluenesulfonamide (8) as pale yellow needles, mp 223-225°C (butanone). IR: 1660 cm^{-1}; NMR(δ,d_6-DMSO): 2.35(s,3H,CCH_3),4.05(s,3H,NCH_3), 7.15-7.80(two overlapping AA'BB' patterns,J≈9Hz and 10Hz,respectively,8H,phenyl-H), 8.85,9.05(s,1H each,pyridazine-H); Anal.calcd.for $C_{19}H_{16}ClN_3O_3S$: C,56.79; H,4.01; N,10.46. Found: C,56.59; H,4.08; N,10.40. The second fractions gave 70 mg (17%) of N-[5-(4-chlorobenzoyl)-4-pyridazinyl]-N-methyl-4-toluenesulfonamide (5) as yellow crystals, mp 239-240°C (butanone-methanol). IR: 1680 cm^{-1}; NMR(δ,$CDCl_3$): 2.35(s,3H, CCH_3),4.30(s,3H,NCH_3),7.05-7.70(two overlapping AA'BB' patterns,J≈9Hz and 10Hz, respectively,8H,phenyl-H),8.45,9.70(s,1H each,pyridazine-H); Anal.calcd.for $C_{19}H_{16}ClN_3O_3S$: C,56.79; H,4.01; N,10.46. Found: C,56.58; H,4.14; N,10.29.

Ethyl N-[5-(4-chlorobenzoyl)-4-pyridazinyl]carbamate (4)

A solution of 5-(4-chlorobenzoyl)-4-pyridazinecarboxylic acid azide[2] (574 mg, 2 mmol) in absolute ethanol (20 ml) was refluxed for 12 h. After evaporation, the residue was recrystallized from 70% aq. ethanol to yield 440 mg (72%) of colourless needles, mp 153-155°C. IR: 1745,1635 cm^{-1}; NMR(δ,d_6-DMSO): 1.10(t,J=8Hz,3H,CH_3), 4.00(q,J=8Hz,2H,OCH_2),7.55-7.85(AA'BB',J≈8Hz,4H,C_6H_4Cl), 9.00,9.45(s,1H each, pyridazine-H),10.50(broad,1H,NH); Anal.calcd.for $C_{14}H_{12}ClN_3O_3$: C,55.00; H,3.96; N,13.74. Found: C,55.06; H,4.02; N,13.48.

Methylation of 4

The methylation of 4 was carried out as described above, employing 1 mmol of 4, 1.5 mmol of NaH, and 2 mmol of CH_3I. After evaporation of the DMF solution, the residue was dissolved in ethanol (20 ml); 2N NaOH (5 ml) was added and the mixture was heated to 50°C for 3 h. The solution was treated with charcoal, filtered, con-

centrated under reduced pressure, and extracted with CH_2Cl_2. The NMR spectrum of the evaporated organic layer indicated a 5:6 mixture of compounds 7a and 10a (see below).

General Procedure for the Preparation of the Alkylamino Alcohols 13a-c

A suspension of 1 (233 mg, 1 mmol) in the appropriate ortho ester (triethyl orthoformate, -acetate, -propionate; 10 ml) was heated to 160°C for 6 h. After evaporation under reduced pressure, the residue was dissolved in absolute ethanol (10 ml). $NaBH_4$ (76 mg, 2 mmol) was added and the solution was refluxed for 2 h. The pH was adjusted to 1 by addition of 0.5N H_2SO_4. After stirring at room temperature for 3 h, followed by addition of 2N NaOH to pH 8, the mixture was evaporated. The residue was extracted twice with boiling 2-propanol (50 ml); removal of the solvent, followed by recrystallisation gave pure products.

4-Chlorophenyl-(5-methylamino-4-pyridazinyl)methanol (13a), 210 mg (84%), colourless crystals, mp 191-193°C (butanone). NMR(δ,d_6-DMSO): 2.85(d,J=6Hz,s after D_2O addition, 3H,CH_3),5.85(s,1H,Ar(OH)C<u>H</u>),6.35(broad,2H,NH,OH),7.45(s,4H,C_6H_4Cl),8.55,8.60(s, 1H each,pyridazine-H); Anal.calcd.for $C_{12}H_{12}ClN_3O$: C,57.72; H,4.84; N,16.83. Found: C,58.01; H,4.91; N,17.27.

4-Chlorophenyl-(5-ethylamino-4-pyridazinyl)methanol (13b), 205 mg (77%), colourless crystals, mp 165-167°C (acetone). NMR(δ,d_6-DMSO): 1.10(t,J=7Hz,3H,CH_3),3.25(m,after D_2O addition: q,J=7Hz,2H,CH_2),5.85(s,1H,Ar(OH)C<u>H</u>),6.10(t,J=6Hz,1H,NH),6.35(broad, 1H,OH),7.40(s,4H,C_6H_4Cl),8.50,8.60(s,1H each,pyridazine-H); Anal.calcd.for $C_{13}H_{14}ClN_3O\cdot 1/8H_2O$: C,58.70; H,5.40; N,15.80. Found: C,58.57; H,5.32; N,15.87.

4-Chlorophenyl-(5-propylamino-4-pyridazinyl)methanol (13c), 244 mg (88%), colourless crystals, mp 155-156°C (acetone-diisopropyl ether). NMR(δ,d_6-DMSO): 0.80(t,J=7Hz,3H, CH_3),1.50(sx,J=7Hz,2H,$NCH_2C\underline{H}_2$),3.20(m,after D_2O addition: t,J=7Hz,2H,NCH_2),5.90(s, 1H,Ar(OH)C<u>H</u>),6.15(t,J=6Hz,1H,NH),6.45(broad,1H,OH),7.45(s,4H,C_6H_4Cl),8.60,8.70 (s,1H each,pyridazine-H); Anal.calcd.for $C_{14}H_{16}ClN_3O$: C,60.54; H,5.81; N,15.13. Found: C,60.23; H,5.70; N,15.12.

General Procedure for the Preparation of the Alkylamino Ketones 7a-c

To a stirred solution of 13a, 13b, or 13c, respectively, (1 mmol) in 2N H_2SO_4 (10 ml) was added $KMnO_4$ (110 mg, 0.7 mmol) in small portions. After 2 h the mixture was filtered, neutralized by addition of 2N NaOH, and extracted with CH_2Cl_2. The extract was washed with water, dried, and evaporated. Recrystallisation gave pure products.

4-Chlorophenyl-(5-methylamino-4-pyridazinyl)methanone (7a), 215 mg (87%), yellow crystals, mp 150-153°C (toluene). IR: 1620 cm^{-1}; NMR(δ,$CDCl_3$): 3.10(d,J=6Hz,after D_2O addition: s,3H,CH_3),7.35-7.65(AA'BB',J≈8Hz,4H,C_6H_4Cl),8.70(s,overlapped by a broad signal,2H,pyridazine-H,NH),8.95(s,1H,pyridazine-H); Anal.calcd.for $C_{12}H_{10}ClN_3O$: C,58.19; H,4.07; N,16.97. Found: C,58.47; H,4.16; N,17.19.

4-Chlorophenyl-(5-ethylamino-4-pyridazinyl)methanone (7b), 185 mg (71%), yellow crystals, mp 138-140°C (toluene-light petroleum). IR: 1625 cm^{-1}; NMR(δ,$CDCl_3$): 1.35 (t,J=7Hz,3H,CH_3),3.45(m,after D_2O addition: q,J=7Hz,2H,CH_2),7.40-7.65(AA'BB',J≈8Hz, 4H,C_6H_4Cl),8.75(s,overlapped by a broad signal,2H,pyridazine-H,NH),8.95(s,1H,pyridazine-H); Anal.calcd.for $C_{13}H_{12}ClN_3O$: C,59.66; H,4.62; N,16.06. Found: C,59.51; H,4.65; N,15.95.

4-Chlorophenyl-(5-propylamino-4-pyridazinyl)methanone (7c), 201 mg (73%), yellow crystals, mp 108-109°C (toluene-light petroleum). IR: 1625 cm^{-1}; NMR(δ,$CDCl_3$): 1.05 (t,J=7Hz,3H,CH_3),1.75(sx,J=7Hz,2H,$NCH_2\underline{CH_2}$),3.40(q,after D_2O addition: t,J=7Hz,2H, NCH_2),7.40-7.65(AA'BB',J≈8Hz,4H,C_6H_4Cl),8.75(s,overlapped by a broad signal,2H, pyridazine-H,NH),8.95(s,1H,pyridazine-H); Anal.calcd.for $C_{14}H_{14}ClN_3O$: C,60.98; H,5.12; N,15.24. Found: C,61.06; H,5.18; N,15.16.

Phase-Transfer Catalyzed Methylation of 1 — Finely powdered NaOH (80 mg, 2 mmol) was added to a stirred solution of 1 (233 mg, 1 mmol) and tetrabutylammonium bromide (10 mg, 0.03 mmol) in THF (25 ml). The mixture was cooled to 0°C, dimethyl sulfate (127 mg, 1 mmol) was added, and stirring was continued until no more starting material could be detected by TLC (2 h). The residue obtained on evaporation was treated with water and extracted with CH_2Cl_2. The extract was washed with water, dried, and evaporated to give a brown solid which was subjected to column chromatography (eluent: CH_2Cl_2-methanol,98+2). After recrystallisation 75 mg (30%) of 7a were obtained.

5-(4-Chlorobenzoyl)-1-methyl-4(1H)-pyridaziniminium Iodide (9a)

A solution of 1 (233 mg, 1 mmol) and methyl iodide (426 mg, 3 mmol) in acetone (30 ml) was allowed to stand at room temperature for 48 h. The separated solid was recrystallized from aq.ethanol to yield 345 mg (92%) of pale yellow crystals, mp 273-283°C (decomp.). IR: 1635 cm^{-1}; NMR(δ,d_6-DMSO): 4.15(s,3H,CH_3),7.65-8.00 (AA'BB',J≈9Hz,4H,C_6H_4Cl),8.80,9.15(s,1H each,pyridazine-H),9.40(broad,1H,NH),9.70 (broad,1H,NH); Anal.calcd.for $C_{12}H_{11}ClIN_3O$: C,38.37; H,2.95; N,11.19. Found: C,38.24; H,2.94; N,11.21.

1-Benzyl-5-(4-chlorobenzoyl)-4(1H)-pyridaziniminium Bromide (9b)

A solution of 1 (233 mg, 1 mmol) and benzyl bromide (256 mg, 1.5 mmol) in acetone (30 ml) was refluxed for 6 h and left at room temperature for 14 h. The precipitate was recrystallized from aq.ethanol to yield 356 mg (88%) of pale yellow crystals, mp 216-219°C. IR: 1640 cm^{-1}; NMR(δ,d_6-DMSO): 5.60(s,2H,CH_2),7.45(s,5H,C_6H_5),7.65-8.00(AA'BB',J≈9Hz,4H,C_6H_4Cl),8.95(s,1H,pyridazine-H),9.40(s,overlapped by a broad signal,2H,pyridazine-H,NH),9.95(broad,1H,NH); Anal.calcd.for $C_{18}H_{15}BrClN_3O$: C,53.42; H,3.74; N,10.38. Found: C,53.20; H,3.88; N,10.36.

General Procedure for the Preparation of the Pyridazinones 10a,10b

To a solution of 9a (375 mg, 1 mmol) or 9b (404 mg, 1 mmol), respectively, in methanol (50 ml) was added 0.5N NaOH (50 ml), and the mixture was left at room temperature for 24 h. After concentration under reduced pressure, the suspension was extracted with CH_2Cl_2. The extract was washed with water, dried, and evaporated. Recrystallisation from aq.ethanol gave pure products.

5-(4-Chlorobenzoyl)-1-methyl-4(1H)-pyridazinone (10a), 224 mg (90%), colourless needles, mp 215-217°C. IR: 1650-1645,1610 cm^{-1}; NMR(δ,d_6-DMSO): 3.95(s,3H,CH_3), 7.50-7.90(AA'BB',J≈9Hz,4H,C_6H_4Cl),8.00,8.70(s,1H each,pyridazine-H); Anal.calcd. for $C_{12}H_9ClN_2O_2$: C,57.96; H,3.65; N,11.27. Found: C,57.93; H,3.70; N,11.03.

1-Benzyl-5-(4-chlorobenzoyl)-4(1H)-pyridazinone (10b), 266 mg (82%), colourless crystals, mp 129-130°C. IR: 1640,1630,1610 cm^{-1}; NMR(δ,d_6-DMSO): 5.40(s,2H,CH_2), 7.40(s,5H,C_6H_5),7.50-7.85(AA'BB',J≈9Hz,4H,C_6H_4Cl),8.00,8.90(s,1H each, pyridazine-H); Anal.calcd.for $C_{18}H_{13}ClN_2O_2$: C,66.57; H,4.03; N,8.63. Found: C,66.48; H,4.15; N,8.63.

Hydrolysis of 8 to 10a — A solution of 8 (201 mg, 0.5 mmol) in 65% H_2SO_4 (7 ml) was heated to 90°C for 1 h. The mixture was poured on ice and made alkaline by slow addition of 2N NaOH. The resulting suspension was extracted with CH_2Cl_2; the extract was washed with water, dried, and evaporated. Recrystallisation from aq.ethanol afforded 75 mg (60%) of 10a.

5-(4-Chlorobenzoyl)-4(1H)-pyridazinone (11)

A solution of 10b (324 mg, 1 mmol) and anhydrous $AlCl_3$ (533 mg, 4 mmol) in dry toluene (25 ml) was heated to 60°C for 1.5 h. After cooling, water (2 ml) was added; the precipitate (216 mg, 92%) was recrystallized from 2-propanol and subsequently from water to afford colourless needles, mp 252-272°C (decomp.). IR: 1650,1645 cm^{-1}; NMR(δ,d_6-DMSO): 7.50-7.85(AA'BB',J≈9Hz,4H,C_6H_4Cl),8.00,8.55(s,1H each, pyridazine-H),

13.70(broad,1H,OH or NH); Anal.calcd.for $C_{11}H_7ClN_2O_2 \cdot 1/2H_2O$: C,54.22; H,3.31; N,11.50. Found: C,53.96; H,3.06; N,11.11.

Reduction of 2b with Borane-Methyl Sulfide — To a solution of 2b (261 mg, 1 mmol) in dry THF (15 ml) was added dropwise a 2M solution of $(CH_3)_2S \cdot BH_3$ in THF (2 ml, 4 mmol) at 0°C. After refluxing for 3 h, the mixture was cooled to 0°C, methanol (5 ml) was added, and stirring was continued at room temperature for 1 h. Anhydrous hydrogen chloride was bubbled through the solution to attain a pH of < 2, and the resulting mixture was refluxed for 1 h. After cooling, methanol (5 ml) was added and the solvents were removed under reduced pressure. The residue was treated with water, made alkaline (pH 8-9) by addition of 2N NaOH, and extracted with CH_2Cl_2. Evaporation afforded an oil which was subjected to MPLC (column size B, eluent: CH_2Cl_2-methanol, 92+8) to give 50 mg (20%) of 13a, identified by NMR.

Reaction of 13a with Acetic Acid/DCC — A solution of 13a (125 mg, 0.5 mmol), acetic acid (60 mg, 1 mmol), and DCC (155 mg, 0.75 mmol) in butanone (20 ml) was stirred at room temperature for 3 h. DCU was filtered off and the filtrate was evaporated. The residual yellow oil was subjected to MPLC (column size A, eluent: CH_2Cl_2-methanol,97+3) to yield 120 mg (80%) of 4-chlorophenyl-(5-methylamino-4-pyridazinyl)methyl acetate (14)$\cdot 1/2H_2O$ as a glassy, amorphous solid. IR: 1740 cm^{-1}; NMR(δ,$CDCl_3$): 2.15(s,3H,$COCH_3$),2.90(d,J=5Hz,s after D_2O addition,3H,NCH_3),5.30 (broad,1H,NH),6.90(s,1H,Ar(OAc)CH),7.10-7.35(AA'BB',J≈9Hz,4H,C_6H_4Cl),8.65,8.75 (s,1H each,pyridazine-H); Anal.calcd.for $C_{14}H_{14}ClN_3O_2 \cdot 1/2H_2O$: C,55.91; H,5.03; N,13.97. Found: C,55.73; H,5.04; N,13.46.

N-[5-(4-Chlorobenzoyl)-4-pyridazinyl]-N-methylacetamide (6)

A solution of 7a (247 mg, 1 mmol) in acetic anhydride (10 ml) was heated to 100°C for 0.5 h. After evaporation under reduced pressure, the residue was recrystallized from aq. ethanol to give 235 mg (81%) of yellow crystals, mp 155-156°C. IR: 1680, 1670 cm^{-1}; NMR(δ,$CDCl_3$): 2.05(s,3H,$COCH_3$),3.40(s,3H,NCH_3),7.40-7.80(AA'BB',J≈9Hz, 4H,C_6H_4Cl),9.10,9.25(s,1H each,pyridazine-H); Anal.calcd.for $C_{14}H_{12}ClN_3O_2$: C,58.04; H,4.18; N,14.50. Found: C,57.93; H,4.21; N,14.67.

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