Pyridazines. LII [1]. Novel 1,2-Diazine Analogues of 2-Aminobenzophenone *via* Directed Lithiation

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The preparation of novel pyridazine analogues of 2-aminobenzophenone, namely 2-(substituted)aminophenyl 3-pyridazinyl ketones **2**, **3**, **4a,b**, achieved by reaction of methyl 3-pyridazinecarboxylate with *ortho*-lithiated aniline derivatives, is reported.

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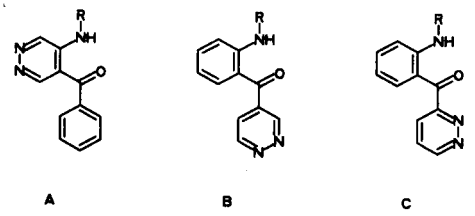
The 2-aminobenzophenone system and heteroaromatic analogues thereof represent valuable synthetic intermediates widely used in the construction of pharmaceutically relevant fused heterocycles. Previously, we succeeded in developing synthetic routes to the first examples of pyridazine congeners, namely 5-(substituted)amino-4-pyridazinyl aryl ketones **A** [3-6] and 2-(substituted)aminophenyl 4-pyridazinyl ketones **B** [7]. Here we report on the preparation of 2-(substituted)aminophenyl 3-pyridazinyl ketones **C**, another novel type of diaza-2-aminobenzophenones.

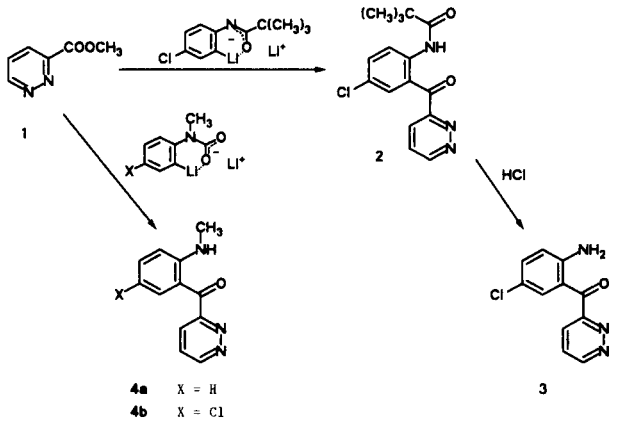
Scheme 1



A B C

For the synthesis of the amino ketone **3**, Gschwend's method of directed lithiation of *N*-pivaloylanilines, followed by reaction with an appropriate electrophile [8], was considered an attractive route. Thus, methyl 3-pyridazinecarboxylate (**1**) [9,10] was reacted with dilithiated 4-chloro-*N*-pivaloylaniline to afford a 50% yield of the ketone **2**

Scheme 2



4a X = H
4b X = Cl

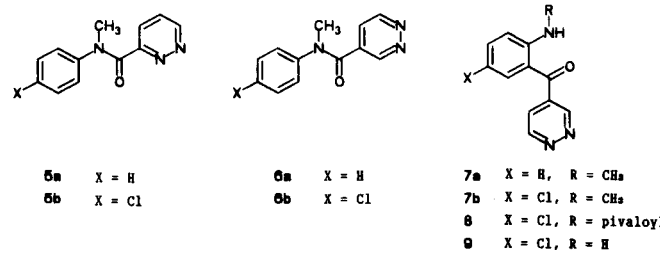
3

which, in turn, could be transformed in high yield into the primary amine **3** upon acidic hydrolysis (Scheme 2). The chloro substituent *para* to the nitrogen atom not only facilitates lithiation of the activated aniline [8], but, additionally, was desirable in view of intended transformations of **3** into 1,4-benzodiazepines: it is well-known that the nature of the substituent in position 7 of the latter class of compounds markedly influences the pharmacological profile [11].

In order to find an access to diaza congeners of 2-(methylamino)benzophenones (compounds **4a,b**), the method for *ortho*-substitution of *N*-monoalkylanilines recently developed by Katritzky [12] was employed. When methyl 3-pyridazinecarboxylate (**1**) was reacted with the *ortho*-lithiated carbamate derived from *N*-methylaniline, the expected 2-methylaminophenyl 3-pyridazinyl ketone **4a** was obtained; similarly, the 5-chloro derivative **4b** could be prepared by employing lithiated lithium *N*-(4-chlorophenyl)-*N*-methylcarbamate as the carbanionic reagent (Scheme 2). In these cases, the modest yields of the target compounds result from incomplete consumption of the starting anilines as well as from formation of several side products.

On attempted replacement of carbon dioxide gas by dry ice in the directed lithiation of 4-chloro-*N*-methylaniline, one of the side products, which turned out to be an isomer of the target compound **4b**, became predominant. Assignment of structure **5b** to this compound [13] is based on its ^{1}H-nmr spectrum (indicating a disubstituted benzene ring and the the lack of H-N-C-H coupling, the latter being

Scheme 3



5a X = H
5b X = Cl

6a X = H
6b X = Cl

7a X = H, R = CH_3
7b X = Cl, R = CH_3
8 X = Cl, R = pivaloyl
9 X = Cl, R = H

typical for alkylamino ketones of type **A**, **B**, and **C**) together with the formation of 3-pyridazinecarboxylic acid [14] upon alkaline hydrolysis.

Application of the procedures used in the syntheses of aryl 3-pyridazinyl ketones **2**, **3**, **4a**,**b** to methyl 4-pyridazinecarboxylate [9], (prepared as described recently [10]) met with limited success: compound **7b** resisted attempted purification owing to instability. However, the directed-lithiation route enabled us to obtain the novel diaza 2-(methylamino)benzophenone **7a**, albeit in moderate yield. The *N*-pivaloylaminoketone **8** was found to be readily accessible; on the other hand, we did not succeed in the isolation of the primary amine **9** after hydrolytic removal of the pivaloyl protecting group [15].

In summary, the described reaction sequences - featuring directed lithiation of aniline derivatives - now permit an access to another novel type of analogues of 2-aminobenzophenones, in which one of the benzene units is replaced by a 1,2-diazine system.

EXPERIMENTAL

Melting points were determined on a Reichert-Kofler hot-stage microscope and are uncorrected. The ir spectra were recorded for potassium bromide pellets on a Jasco IRA-1 spectrophotometer. The ^{1}H-nmr spectra were recorded on a Bruker AC 80 (80 MHz) spectrometer (TMS as the internal reference). Mass spectra were obtained on a Varian MAT 311A instrument (70 eV). For tlc, Merck aluminium sheets pre-coated with Kieselgel 60 F_{254} were used; column chromatography was carried out on Merck Kieselgel 60 (70-230 mesh), medium-pressure liquid chromatography (mplc) was performed on Merck LiChroprep Si 60 (230-400 mesh), detection at 280 nm. All reactions employing organolithium reagents were carried out under dry argon. Tetrahydrofuran was dried by passing through a column of alumina (activity I, basic); light petroleum refers to the fraction of bp 50-70°.

5-Chloro-2-(pivaloylamino)phenyl 3-Pyridazinyl Ketone (**2**).

To a solution of 847 mg (4 mmoles) of 4-chloro-*N*-pivaloylaniline in 12 ml of dry tetrahydrofuran were added dropwise at 0° 5.5 ml (8.8 mmoles) of a 1.6*M* solution of *n*-butyllithium in hexane, and the mixture was stirred at 0° for 2 hours. It was then added dropwise at −70° to a solution of 552 mg (4 mmoles) of methyl 3-pyridazinecarboxylate (**1**) [9,10] in 20 ml of dry tetrahydrofuran. Stirring was continued for 1 hour at −70° and for 16 hours at room temperature. After addition of 10 ml of water, the mixture was concentrated *in vacuo*; the residue was treated with water and extracted with dichloromethane. Evaporation of the extract, followed by column chromatography (dichloromethane-ethyl acetate, 9:1) and subsequent recrystallisation from ethyl acetate-light petroleum afforded 635 mg (50%) of pale yellow crystals, mp 168°; ^{1}H-nmr (deuteriochloroform): δ 11.24 (br, NH, 1 H), 9.38 (dd, J_{4-6} = 1.8 Hz, J_{5-6} = 4.9 Hz, pyridazine H-6, 1 H), 8.79 (d, J_{3-4} = 9.1 Hz, benzene H-3, 1 H), 7.50-8.12 (m, benzene H-4, H-6; pyridazine H-4, H-5; 4 H), 1.36 (s, CH_3, 9 H); ir: cm^{-1} 3300 (NH), 1680 (C=O), 1630 (C=O).

Anal. Calcd. for $C_{16}H_{16}ClN_3O_2$: C, 60.48; H, 5.08; N, 13.22. Found: C, 60.38; H, 5.14; N, 13.19.

5-Chloro-2-(pivaloylamino)phenyl 4-Pyridazinyl Ketone (**8**).

The preparation was accomplished as described for compound **2**, employing 552 mg (4 mmoles) of methyl 4-pyridazinecarboxylate [9,10] as the electrophile. Column chromatography (dichloromethane-ethyl acetate, 9:1), followed by recrystallisation from ethyl acetate-light petroleum gave 547 mg (43%) of colorless crystals, mp 130-134°; ^{1}H-nmr (deuteriochloroform): δ 11.01 (br, NH, 1 H), 9.40-9.53 (m, pyridazine H-3, H-6, 2 H), 8.80 (d, J_{3-4} = 9.1 Hz, benzene H-3, 1 H), 7.38-7.70 (m, benzene H-4, H-6, pyridazine H-5, 3 H), 1.36 (s, CH_3, 9 H); ir: cm^{-1} 3240 (NH), 1670 (C=O).

Anal. Calcd. for $C_{16}H_{16}ClN_3O_2$: C, 60.48; H, 5.08; N, 13.22. Found: C, 60.37; H, 5.12; N, 13.27.

2-Amino-5-chlorophenyl 3-Pyridazinyl Ketone (**3**).

A solution of 317 mg (1 mmole) of the anilide **2** in 15 ml of 6*M* hydrochloric acid was heated to 80° for 3 hours. After cooling, the mixture was neutralized with 2*M* sodium hydroxide and then exhaustively extracted with dichloromethane. Evaporation of the extract, followed by recrystallisation from ethyl acetate-light petroleum afforded 203 mg (87%) of yellow crystals, mp 172°; ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 9.41 (dd, J_{4-6} = 2.3 Hz, J_{5-6} = 4.5 Hz, pyridazine H-6, 1 H), 7.83-8.13 (m, pyridazine H-4, H-5, 2 H), 7.30-7.60 (br, overlapped by m, NH_2, benzene H-4, H-6, 4 H), 6.95 (d, J_{3-4} = 8.9 Hz, benzene H-3, 1 H); ir: cm^{-1} 3440 (NH), 3300 (NH), 3160 (NH), 1615 (C=O).

Anal. Calcd. for $C_{11}H_8ClN_3O$: C, 56.54; H, 3.45; N, 17.98. Found: C, 56.31; H, 3.54; N, 17.79.

2-(Methylamino)phenyl 3-Pyridazinyl Ketone (**4a**).

To a solution of 428 mg (4 mmoles) of *N*-methylaniline in 15 ml of dry tetrahydrofuran were added dropwise at −70° 2.5 ml (4 mmoles) of a 1.6*M* solution of *n*-butyllithium in hexane. The mixture was stirred at −70° for a few minutes, then it was allowed to come to room temperature. Dry carbon dioxide gas was bubbled through the mixture for 10-15 minutes. Then the solvent was evaporated and a pale yellow residue (lithium *N*-phenyl-*N*-methylcarbamate) was obtained, which was again dissolved in 13 ml of dry tetrahydrofuran and cooled to −70°. Then 2.8 ml (4.8 mmoles) of a 1.7*M* solution of *t*-butyllithium in pentane was added slowly, and the color became bright yellow. The dry-ice cooling bath was replaced by an ice-salt bath, the solution was kept at −20° for 1 hour and then was added dropwise to a solution of 552 mg (4 mmoles) of methyl 3-pyridazinecarboxylate [9,10] (**1**) in 20 ml of dry tetrahydrofuran. The mixture was stirred for 2 hours at −70°, then it was allowed to regain room temperature over a period of several hours. After addition of saturated aqueous ammonium chloride, the mixture was stirred for 10 minutes, then it was diluted with diethyl ether. The organic layer was separated, washed with brine, dried, and evaporated. The residue was subjected to column chromatography (dichloromethane-ethyl acetate, 1:2). After elution of unreacted *N*-methylaniline, the first main fraction gave 250 mg (29%) of compound **4a** as yellow crystals, mp 140-142° (from ethyl acetate-light petroleum); ^{1}H-nmr (deuteriochloroform): δ 9.29 (dd, J_{4-6} = 1.9 Hz, J_{5-6} = 4.8 Hz, pyridazine H-6, 1 H), 8.85 (br, NH, 1 H), 7.34-7.93 (m, benzene H-4, H-6, pyridazine H-4, H-5, 4 H), 6.48-6.84 (m, benzene H-3, H-5, 2 H), 3.02 (d, J = 4.5 Hz, s after addition of deuterium oxide, CH_3, 3 H); ir: cm^{-1} 3360 (NH), 1620 (C=O).

Anal. Calcd. for $C_{12}H_{11}N_3O$: C, 67.59; H, 5.20; N, 19.71. Found: C, 67.53; H, 5.09; N, 19.63.

After elution of several minor fractions (containing unidenti-

fied side products), the second main fraction was collected and further purified by mplc (dichloromethane-ethyl acetate, 1:1) to afford 60 mg (7%) of *N*-methyl-*N*-phenyl-3-pyridazinecarboxamide (**5a**) as colorless crystals, mp 117-118° (from ethyl acetate-light petroleum); ^{1}H-nmr (deuteriochloroform): δ 9.01 (dd, J_{4-6} = 2.0 Hz, J_{5-6} = 4.8 Hz, pyridazine H-6, 1 H), 7.00-7.75 (m, C_6H_5, pyridazine H-4, H-5, 7 H), 3.56 (s, CH_3, 3 H); ir: cm^{-1} 1650 (C=O).

Anal. Calcd. for $C_{12}H_{11}N_3O$: C, 67.59; H, 5.20; N, 19.71. Found: C, 67.61; H, 5.27; N, 19.85.

2-(Methylamino)phenyl 4-Pyridazinyl Ketone (**7a**).

The preparation was accomplished as described for compound **4a**, employing 552 mg (4 mmoles) of methyl 4-pyridazinecarboxylate [9,10] as the electrophile. Column chromatography (dichloromethane-ethyl acetate, 1:2) afforded 120 mg (14%) of compound **7a** as yellow crystals, mp 139-140° (from ethyl acetate-light petroleum); ^{1}H-nmr (deuteriochloroform): δ 9.30-9.40 (m, pyridazine H-3, H-6, 2 H), 8.78 (br, NH, 1 H), 7.22-7.62 (m, benzene H-4, H-6, pyridazine H-5, 3 H), 6.47-6.87 (m, benzene H-3, H-5, 2 H), 3.01 (d, J = 5.1 Hz, s after addition of deuterium oxide, CH_3, 3 H); ir: cm^{-1} 3320 (NH), 1610 (C=O).

Anal. Calcd. for $C_{12}H_{11}N_3O$: C, 67.59; H, 5.20; N, 19.71. Found: C, 67.45; H, 5.10; N, 19.56.

Further elution gave 80 mg (9%) of *N*-methyl-*N*-phenyl-4-pyridazinecarboxamide (**6a**) as colorless needles, mp 96-97° (from ethyl acetate-light petroleum); ^{1}H-nmr (deuteriochloroform): δ 8.95-9.10 (m, pyridazine H-3, H-6, 2 H), 6.95-7.35 (m, C_6H_5, pyridazine H-5, 6 H), 3.52 (s, CH_3, 3 H); ir: cm^{-1} 1635 (C=O).

Anal. Calcd. for $C_{12}H_{11}N_3O$: C, 67.59; H, 5.20; N, 19.71. Found: C, 67.38; H, 5.26; N, 19.72.

5-Chloro-2-(methylamino)phenyl 3-Pyridazinyl Ketone (**4b**).

The preparation was accomplished as described for compound **4a**, employing 566 mg (4 mmoles) of 4-chloro-*N*-methylaniline instead of *N*-methylaniline as the starting material. Column chromatography (dichloromethane-ethyl acetate, 1:2) afforded 149 mg (15%) of compound **4b** as yellow crystals, mp 106-108° (from diisopropyl ether); ^{1}H-nmr (deuteriochloroform): δ 9.30 (dd, J_{4-6} = 1.9 Hz, J_{5-6} = 4.9 Hz, pyridazine H-6, 1 H), 8.83 (br, NH, 1 H), 7.27-7.95 (m, benzene H-4, H-6, pyridazine H-4, H-5, 4 H), 6.73 (d, J_{3-4} = 9.1 Hz, benzene H-3, 1 H), 3.00 (d, J = 5.1 Hz, s after addition of deuterium oxide, CH_3, 3 H); ir: cm^{-1} 3320 (NH), 1610 (C=O).

Anal. Calcd. for $C_{12}H_{10}ClN_3O$: C, 58.19; H, 4.07; N, 16.97. Found: C, 58.10; H, 3.98; N, 16.91.

Further elution gave 100 mg (10%) of *N*-(4-chlorophenyl)-*N*-methyl-3-pyridazinecarboxamide (**5b**) as colorless crystals, mp 94-96° (from ethyl acetate-light petroleum); ^{1}H-nmr (deuteriochloroform): δ 9.05 (X-part of an ABX system, J_{4-6} = 1.5 Hz, J_{5-6} = 4.9 Hz, pyridazine H-6, 1 H), 7.68-7.81 (B-part of an ABX system, J_{4-5} = 8.4 Hz, J_{4-6} = 1.5 Hz, pyridazine H-4, 1 H), 7.37-7.54 (A-part of an ABX system, J_{4-5} = 8.4 Hz, J_{5-6} = 4.9 Hz, pyridazine H-5, 1 H), 7.00-7.28 (AA'BB' system, C_6H_4Cl, 4 H), 3.54 (s, CH_3, 3 H); ir: cm^{-1} 1640 (C=O); ms: m/e 247, 249 (M$^+$, 60, 19), 140 (36), 120 (50), 107 (57), 51 (100).

Anal. Calcd. for $C_{12}H_{10}ClN_3O$: C, 58.19; H, 4.07; N, 16.97. Found: C, 58.37; H, 4.08; N, 16.78.

5-Chloro-2-(methylamino)phenyl 4-Pyridazinyl Ketone (**7b**).

The preparation was accomplished as described for compound **4b**, employing 552 mg (4 mmoles) of methyl 4-pyridazinecarboxylate [9,10] as the electrophile. Column chromatography (dichloromethane-ethyl acetate, 1:2) afforded 425 mg (43%) of compound **7b** as an unstable, amorphous yellow solid which decomposed on attempted purification; ^{1}H-nmr (deuteriochloroform): δ 9.30-9.45 (m, pyridazine H-3, H-6, 2 H), 8.75 (br, NH, 1 H), 7.57 (dd, J_{3-5} = 2.3 Hz, J_{5-6} = 5.1 Hz, pyridazine H-5, 1 H), 7.20-7.45 (m, benzene H-4, H-6, 2 H), 6.77 (d, J_{3-4} = 9.2 Hz, benzene H-3, 1 H), 3.01 (d, J = 5.0 Hz, s after addition of deuterium oxide, CH_3, 3 H).

Further elution gave 109 mg (11%) of *N*-(4-chlorophenyl)-*N*-methyl-4-pyridazinecarboxamide (**6b**) as colorless crystals, mp 98-99° (from ethyl acetate-light petroleum); ^{1}H-nmr (deuteriochloroform): δ 9.12 (dd, J_{3-6} = 0.9 Hz, J_{5-6} = 5.3 Hz, pyridazine H-6, 1 H), 9.00 (dd, J_{3-5} = 3.2 Hz, J_{3-6} = 0.9 Hz, pyridazine H-3, 1 H), 7.20-7.35 (BB'-part of an AA'BB' system, overlapped by dd, pyridazine H-5; C_6H_4Cl; 3 H), 6.94-7.09 (AA'-part of an AA'BB' system, J_{A-B} = 8.7 Hz, C_6H_4Cl, 2 H), 3.49 (s, CH_3, 3 H); ir: cm^{-1} 1655 (C=O); ms: m/e 247, 249 (M$^+$, 59, 19), 140 (100), 80 (70).

Anal. Calcd. for $C_{12}H_{10}ClN_3O$: C, 58.19; H, 4.07; N, 16.97. Found: C, 58.35; H, 4.09; N, 16.75.

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[13] An analogous compound **5a** was isolated as side product in the course of the preparation of **4a**. Formation of similar anilides **6a,b** was also observed on employment of methyl 4-pyridazinecarboxylate as the electrophile.

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[15] Tlc monitoring indicated the formation of a product of the expected retention behaviour, which however, underwent further transformations on attempted isolation. In this connection, the recently observed [7] intramolecular S_N^H reaction of closely related 2-(alkylamino)phenyl 4-pyridazinyl ketones should be emphasized.