ORTHODOX-DIRECTED METALATION OF 3-HETEROSUBSTITUTED 4-METHYL-6-PHENYL-PYRIDAZINES

Jean-Marie Sitamzé, André Mann*, and Camille-Georges Wermuth

Laboratoire de Pharmacochimie Moléculaire Centre de Neurochimie du CNRS, 5, rue Blaise Pascal, 67084 Strasbourg-Cedex, France

Abstract - Side-chain metalation of 4-methyl-6-phenyl pyridazines (2-4) with lithium diisopropylamide or 2,2,6,6-tetramethylpiperidide and subsequent alkylation with various electrophiles have been investigated. Depending on the substituent attached at the 3-position (Cl, OMe or NHCOtBu), the preparation of the alkylated pyridazines was more or less efficient.

The pyridazine derivatives continue to stimulate a great deal of interest, as demonstrated by two recent reviews devoted to their chemical and biochemical properties.\textsuperscript{1,2} Over the years in our group we used largely the pyridazine nucleus as core to design potent compounds in several area of medicinal chemistry. In our hands specially the 3-amino-4-methyl-6-phenylpyridazine (1) proved to be of exceptional value. Depending on the nature or/and the position of the appendages, we could produce such diverse compounds as antidepressants,\textsuperscript{3,4} GABA antagonists\textsuperscript{5} or muscarine agonists.\textsuperscript{6} During our investigations on structure-activity relationships, we needed to prepare analogues bearing various alkyl groups in the 4 position. As the access to this class of compounds needed a tedious ring elaboration,\textsuperscript{7} we became interested in a more convenient approach. From a literature survey it appeared that ortho directed metalation can offer routes to chain extension if the methylene anion in the 4-methylpyridazine would be accessible.\textsuperscript{8} In fact the incorporation of various electrophiles in \( \pi \)-deficient heterocycles after ortho-lithiation has been reported,\textsuperscript{9-11} and benzylic anions are readily accessible from heteroatom directed lithiation of the corresponding tolyl derivatives.\textsuperscript{12,13} Therefore we decided to prepare the pyridazines (2, 3 and 4) in order to investigate their metalation and reactivity, regarding the different lithiation-directing groups in the \( \alpha \) position to a ring nitrogen (Scheme 1). Herein we report that treatment of compounds (2, 3 and 4) with lithium diisopropylamide
(LDA) or 2,2,6,6-tetramethylpiperidide (LTMP) generates the expected methylene anion (A) which reacts cleanly with various electrophiles (halides or carbonyls) in moderate to satisfactory yields.

![Diagram showing molecules 1, 2, 3, and 4 with structural formulas and labels X = NH₂, Cl, OMe, NHCOBu⁻]

| 1 | X = NH₂ |
| 2 | Cl      |
| 3 | OMe     |
| 4 | NHCOBu⁻ |

Scheme 1

The synthesis of the pyridazines (2-4) was performed starting from the easily accessible pyridazinone (5)⁴,⁵ which afforded the imino chloride (2) after treatment with POCl₃ in 95% yield.⁴,⁵ The chloropyridazine (2) was converted to the methoxypyridazine (3) in 90% yield with sodium methoxide in hot DMF. Finally the pivaloyl amide (4) was obtained via our newly reported synthesis of 3-aminopyridazine,¹⁴ followed by an acylation with pivaloyl chloride/triethylamine in tetrahydrofuran (Scheme 2).

![Diagram showing the synthesis of pyridazines 2, 3, and 4]

Reagents: i) POCl₃; ii) MeONa, DMF; iii) NH₂NH₂; iv) Raney Ni; v) pivaloyl chloride, TEA.

Scheme 2

The results of metalation experiments employing LDA or LTMP agents together with the products obtained after quenching with alkyl halides, aldehydes or ketones are collected in Scheme 3. After some experimentations we found that the use of two equivalents of metalating agent for the reaction with halides and 4 equivalents for the reaction with aldehydes or ketones, gave the best results. A complexation process may explain this experimental observation.
Concerning the alkylation of chloropyridazine (2) the reaction gave low yields with bromobutane and phenethyl bromide; attempts to increase the yield by adding HMPT or to change the base were unsuccessful. This result is not so surprising if one considers that the pyridazine nucleus is π-deficient and therefore prone to undergo nucleophilic substitution, the presence of the chlorine contributes to enhance this character. Albeit the low yields 18% and 20% respectively, compounds (2a) and (2b) could be purified and identified after column chromatography. In contrast with these results the alkylation of methoxypyridazine (3) with phenethyl bromide and 3-phenylpropionaldehyde afforded compounds (3b) and (3c) in respectively 89% and 51% yields. Finally, the alkylation of pyridazine (4) proceeded cleanly with phenethyl bromide, 3-phenylpropionaldehyde and benzophenone. The obtained compounds (4b, 4c and 4d) could be purified by chromatography on silica gel. Taking together our results on the alkylation of 2, 3 and 4 it appears that the heteroatoms (O or N) develop chelation and allow the regioselective substitution. Thus the lithiation of 4-methylpyridazine using LTMP could be a practical method for the preparation of substituted pyridazines. As we were mainly interested in 4-alkyl-3-aminopyridazines, compounds (4a-d), provide, after mild hydrolysis of the pivaloyl protecting group, a simple and convergent route towards this class of compounds.

EXPERIMENTAL

$^1$H Nmr spectra were performed on a Bruker AC 200 (200 MHz) spectrometer using Me$_4$Si as internal reference. Melting points were measured in open capillary tubes using a Gallenkamp
apparatus, and are uncorrected. Purifications and separations by column chromatography were performed on silica gel, using the flash chromatography procedure. Ether and THF were distilled from sodium ketyl under argon. All reactions involving metellation were performed under argon.

3-Chloro-4-methyl-6-phenylpyridazine (2)
A mixture of 4-methyl-6-phenylpyridazin-3(2H)-one (3)\(^4\) (6 g, 0.032 mol) and POCI\(_3\) (25 ml, 0.26 mol) was heated at 80°C for 3 h. Excess of POCI\(_3\) was evaporated in vacuo, the residue triturated with cold water and neutralized with 33 % NaOH. The obtained solid was filtered and recrystallized from isopropanol to afford 2 (5.22 g, 95 %), mp 142°C, lit.,\(^4\) mp 142°C.

3-Methoxy-4-methyl-6-phenylpyridazine (3)
Compound (2) (10 g, 0.049 mol) was dissolved in dimethylformamide (30 ml) and a solution of sodium methoxide [prepared from anhydrous methanol (20 ml) and sodium (1.12 g, 0.04 mol)] was added. The mixture was refluxed for 12 h, thereafter poured into H\(_2\)O (500 ml) and extracted with dichloromethane. The organic layer was dried (Na\(_2\)SO\(_4\)) and concentrated in vacuo. The obtained solid was recrystallized from hexane to afford 3 (8.8 g, 90 %), mp 59°C; \(^1\)H nmr (200 MHz, CDCl\(_3\)) \(\delta\) 2.29 (s, 3H, CH\(_3\)), 4.19 (s, 3H, OCH\(_3\)), 7.45-7.51 (m, 3H), 7.59 (s, 1H), 7.97-8.02 (m, 2H). Anal. Calcd for C\(_{12}\)H\(_{12}\)N\(_2\)O: C, 71.97; H, 6.04; N, 13.99. Found : C, 71.70 ; H, 6.00 ; N, 13.90.

3-(N-Pivaloylamino)-4-methyl-6-phenylpyridazine (4)
To an ice cooled suspension of 1\(^{14}\) (2 g, 0.011 mol) and triethylamine (2.45 ml, 0.0176 mmol) in dry THF (15 ml) was added dropwise a solution of pivaloyl chloride (2.15 ml, 0.0176 mmol) in THF (15 ml). The mixture was stirred at room temperature for 2 h. Then the solvent was removed in vacuo. The residue was taken up in dichloromethane (50 ml), washed with 0.2 N NaOH and water. The organic layer was dried (Na\(_2\)SO\(_4\)) and evaporated in vacuo. Purification by chromatography on silica gel (CH\(_2\)Cl\(_2\)-AcOEt: 8-2) gave colourless crystals of 4 (1.5 g, 51 %), mp 203-204°C; \(^1\)H nmr (200 MHz, CDCl\(_3\)) \(\delta\) 1.41 (s, 9H), 2.35 (s, 3H), 7.49-7.48 (m, 3H), 7.60 (s, 1H), 8.01-8.07 (m, 2H), 8.89 (s, 1H). Anal. Calcd for C\(_{16}\)H\(_{19}\)N\(_3\)O : C, 71.34 ; H, 7.10 ; N, 15.60. Found : C, 70.90 ; H, 7.00 ; N, 15.60.

General procedure for metalation of compounds (2-4)

Experiment for 1 mmol of pyridazine
Lithium diisopropylamide or 2,2,6,6-tetramethylpiperidide were prepared in dry THF (15 ml) by adding a solution of 2 M BuLi in hexane at -30°C. Then the mixture was stirred at 0°C for 30 min. When the electrophile was an halide 2 eq. of base were used, in the case of an aldehyde or a ketone 4 eq. were used. A solution of pyridazines (2-4) (1 eq.) in THF (5 ml) was added at -78°C
to the metalating agent. After stirring the mixture for 1.5 h at -70°C, a solution of the electrophile (1 eq.) in THF (5 ml) was added via a syringe. The reaction was left overnight at room temperature. After cooling at 0°C, the reaction was quenched successively with 11 N HCl (2 ml), ethanol (5 ml) and THF (5 ml). A saturated solution of NaHCO₃ was added, until neutralization. The mixture was evaporated in vacuo to give an aqueous residue. This residue was extracted with dichloromethane (3 x 90 ml). The organic layer was dried (Na₂SO₄) and evaporated in vacuo. The obtained residue was purified by column chromatography (CH₂Cl₂-AcOEt: 6-4) on silica gel.

3-Chloro-6-phenyl-4-pentylpyridazine (2a)
Yield: 18%; mp 40-41°C; ¹H nmr (200 MHz) δ 0.91 (t, J=6.70 Hz, 3H), 1.42-1.35 (m, 4H) 1.72-1.61 (m, 2H), 2.74 (t, J=8 Hz, 2H), 7.49-7.46 (m, 3H), 7.65 (s, 1H), 8.03-7.98 (m, 2H). Anal. Calcd for C₁₅H₁₇N₂Cl: C, 69.07; H, 6.57; N, 10.70. Found C, 68.60; H, 6.50; N, 10.70.

3-Chloro-6-phenyl-4-(3'-phenylpropyl)pyridazine (2b)
Yield: 20%; mp 96%; ¹H nmr (200 MHz) δ 2.15-2.03 (m, 2H), 2.86-2.74 (m, 4H); 7.36-7.20 (m, 5H), 7.51-7.48 (m, 3H), 7.64 (s, 1H) 8.05-8.00 (m, 2H). Anal. Calcd for C₁₉H₁₇N₂Cl: C, 73.88; H, 5.54; N, 9.05. Found C, 73.90; H, 5.50; N, 8.90.

3-Methoxy-6-phenyl-4-(3'-phenylpropyl)pyridazine (3b)
Yield: 89%; oil; ¹H nmr (200 MHz) δ 2.02-2.05 (m, 2H), 2.75-2.75 (m, 4H), 4.20 (8, 3H), 7.23-7.28 (m, 5H), 7.46-7.50 (m, 3H), 7.56 (s, 1H), 7.96-8.03 (m, 2H). Anal. Calcd for C₂₀H₂₀N₂O: C, 78.91; H, 6.62; N, 9.20. Found C, 78.60; H, 6.20; N, 8.80.

3-3'-Ethoxy-6-phenyl-4-(2'-hydroxy-4'-phenylbutyl)pyridazine (3c)
Yield: 51%; mp 120-121°C; ¹H nmr (200 MHz) δ 1.85 (m, 2H), 1.93-2.06 (m, 2H), 2.65-2.74 (m, 4H), 7.14-7.29 (m, 5H), 7.49-7.52 (m, 3H), 7.71 (s, 1H), 8.05-8.20 (m, 2H), 8.47 (s, 1H). Anal. Calcd for C₂₁H₂₂N₂O₂: C, 75.45; H, 6.58; N, 8.38. Found C, 75.60; H, 6.20; N, 8.10.

3-(N-Pivaloylamino)-6-phenyl-4-(3'-phenylpropyl)pyridazine (4b)
Yield: 60%; mp 140°C; ¹H nmr (200 MHz) δ 1.36 (s, 9H), 1.93-2.06 (m, 2H), 2.65-2.74 (m, 4H), 7.14-7.29 (m, 5H), 7.49-7.52 (m, 3H), 7.71 (s, 1H), 8.05-8.20 (m, 2H), 8.47 (s, 1H). Anal. Calcd for C₂₄H₂₇N₃O: C, 77.21; H, 7.23; N, 11.25. Found C, 76.95; H, 7.20; N, 11.40.

3-(N-Pivaloylamino)-4-(2'-hydroxy-4'-phenylbutyl)-6-phenylpyridazine (4c)
Yield: 80%; mp 179°C; ¹H nmr (200 MHz) δ 1.34 (s, 9H), 1.80 (m, 2H), 2.70-2.90 (m, 4H), 3.18 (d, J=4.5 Hz, exch, 1H), 4.20-4.25 (m, 1H), 7.22-7.34 (m, 5H), 7.45-7.48 (m, 3H), 7.70 (s, 1H), 7.93-7.97 (m, 2H), 8.85 (s, 1H). Anal. Calcd for C₂₅H₂₉N₃O₂: C, 74.44; H, 7.19; N, 10.42. Found C, 74.64; H, 7.20; N, 10.72.
3-(N-Pivaloylamino)-4-(2', 2'-diphenyl-2'-hydroxyethyl)-6-phenylpyridazine (4d)

Yield: 91%; mp 166°C; 1H nmr (200 MHz) δ 1.33 (s, 9H), 3.64 (s, exch. 1H), 3.84 (s, 2H), 7.49-7.06 (m, 15H), 7.52 (s, 1H), 8.50 (s, 1H). Anal. Calcd for C_{29}H_{29}N_{3}O_{2}: C, 77.13; H, 6.47; N, 9.30. Found C, 77.40; H, 6.20; N, 9.10.

REFERENCES

15. Hydrolysis conditions are for 1 mmol of pivaloylamide: THF (5 ml) and 1 N HCl (2.5 ml) at reflux for 10 h.

Received, 20th January, 1994