A New Route to Arglecin by Metalation and Cross Coupling of Pyrazines. Metalation of Diazines. XII

A. Turck, N. Plé, D. Dognon, C. Harmoy and G. Quéguiner*

Laboratoire de Chimie Organique Fine et Hétérocyclique del'IRCOF,
URA CNRS 1429, Institut National des Sciences Appliquées de Rouen,
BP 08, 76131 Mont Saint Aignan Cedex, France

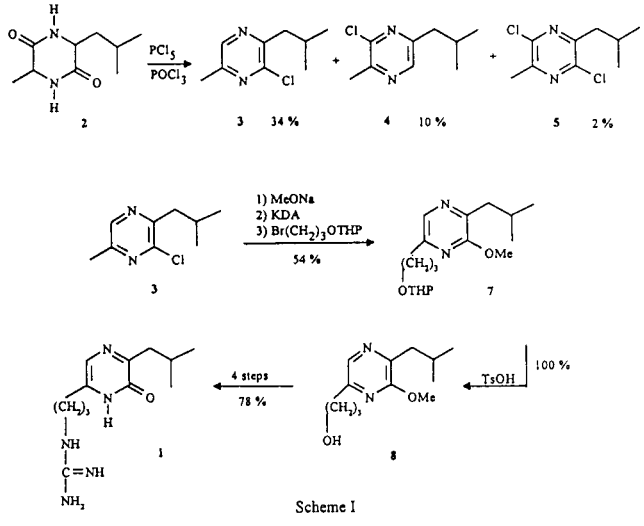
Received April 25, 1994

The metalation of dihalogeno and halogenomethoxypyrazines was performed. The resulting pyrazines were submitted to a cross-coupling reaction with propargyl alcohol followed, after dehydration, by a catalytic reduction. This gives a new route to the synthesis of a key intermediate in the synthesis of arglecin.

J. Heterocyclic Chem., **31**, 1449 (1994).

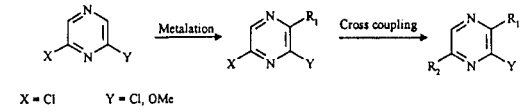
Arglecin (**1**) has been extracted from cultures of *streptomyces* and *lavandurae* and it exhibits antiarythmic properties.

A synthetic route has been developped by Ohta *et al.* [1, 2] (Scheme I).



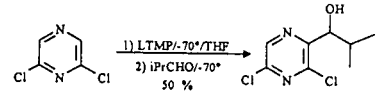
Scheme I

The first step of this synthesis starting from DL-alanyl leucyl anhydride (**2**) was a reaction of **2** with phosphorus chlorides affording three chloro derivatives **3, 4, 5** which were separated by preparative liquid chromatography, The following steps presented good yields. Our experience in directed metalation of pyrazine [3] prompted us to investigate a new route to prepare compound **8** which is a key intermediate in the synthesis of arglecin (**1**). This route avoids the first step of the preceding synthesis which afforded three chloro derivatives. Our strategy is based on metalation and cross coupling reactions (Scheme II).



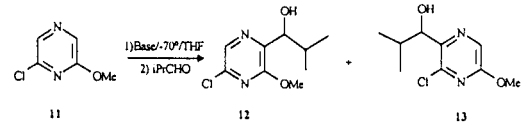
Scheme II

The most readily available 2,6-disubstituted pyrazine is the dichloropyrazine which is commercial. So its metalation was performed and isobutanal was reacted (Scheme III).



Scheme III

The use of a symmetrically 2,6-disubstituted pyrazine like **9** skipped problems of metalation regioselectivity but the yield was medium. In the diazine series the methoxy group proved to be a good *ortho* directing group for metalation [4]; so the 2-chloro-6-methoxypyrazine (**11**) was easily synthethized from **9** and submitted to the metalation reaction (Scheme IV).



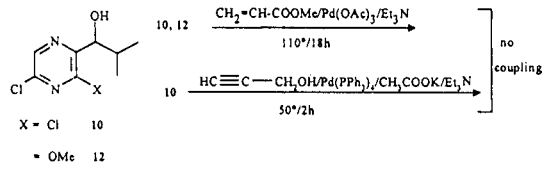
Scheme IV

Base	Yield	ratio 12:13
LTMP	57%	85/15
LDA	90%	87/13

The yield was good with LDA and the regioselectivity acceptable. The correct identification of the two isomers **12** and **13** has been much more difficult than expected. The ^{1}H nmr chemical shifts of pyrazine hydrogens of 2,6-dichloro and 2,6-dimethoxypyrazine are strongly different (8.5 and 7.8 ppm) but for the 2-chloro-6-methoxypyrazine (**11**) the two hydrogen shifts are almost identical at 8.1 and 8.11 ppm, so the two isomers could not be distinguished by simple ^{1}H nmr. The use of the Nuclear Overhauser Effect on the methoxy group allowed us to ensure that the main isomer was **12**. The correct ratio between **12** and **13** was then found by use of hplc.

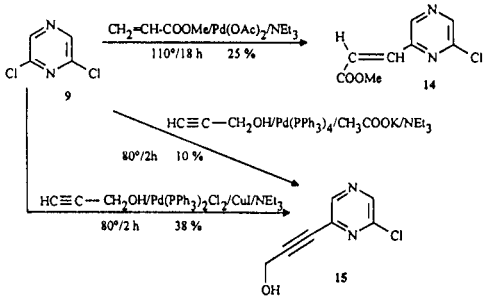
Then the coupling reaction was tested with **10** and the

mixture of **12** and **13**. In the literature there are some references dealing with the coupling of diazines with acetylenes [5-10] but few with ethylenes [11-14].



Scheme V

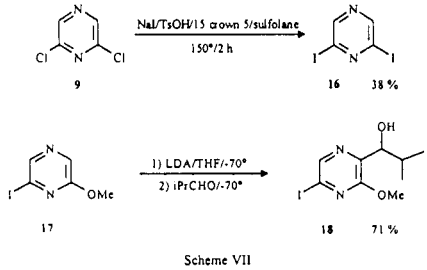
Suitable reaction conditions were derived from the literature [7, 12] but gave no results (Scheme V).



Scheme VI

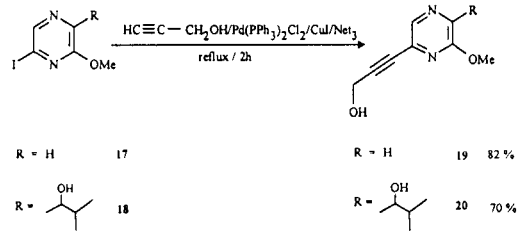
In order to test the feasibility of the coupling with chlorine atoms on simpler molecules, 2,6-dichloropyrazine was coupled with methyl acrylate and propargyl alcohol (Scheme VI),

With propargyl alcohol an increase in the reaction time to 6 hours gave no substantial increase of the yield. The coupling reaction tested with 2,6-dichloropyrazines afforded low yields thus was necessary to use a more reactive halogen. The synthesis of 2,6-diiodopyrazine (**16**) was described by Street [15] (Scheme VII) but the yield was poor (34%) and the reaction very slow (4 days). Various reaction conditions were tested and if the yield could not be significantly increased, we succeeded to diminish the reaction time by a substantial amount by using a higher temperature and sulfolane as the solvent. The diiodo derivative **16** was reacted with sodium methylate to afford compound **17** with a quantitative yield, then the metalation was performed (Scheme VII).



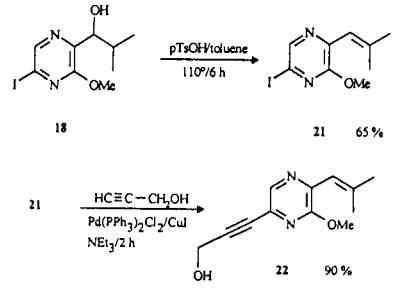
Scheme VII

Coupling of **17** and **18** with propargyl alcohol was successful (Scheme IX).



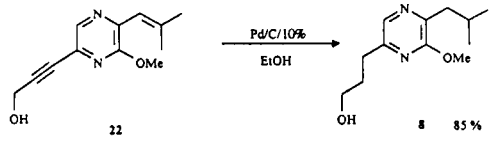
Scheme IX

To prepare compound **8** it was now necessary to reduce the benzylic type alcohol and the triple bond of **20**. In some cases the reduction of such benzylic alcohols can be difficult. So various reduction methods were tested on compounds **10** and **18** and on 2-chloro-3-(1-hydroxybenzyl)pyrazine, these are described in the experimental. These reactions were unsuccessful so another strategy was devised based on the dehydration of **18** and the coupling of the dehydrated compound **21** (Scheme X).



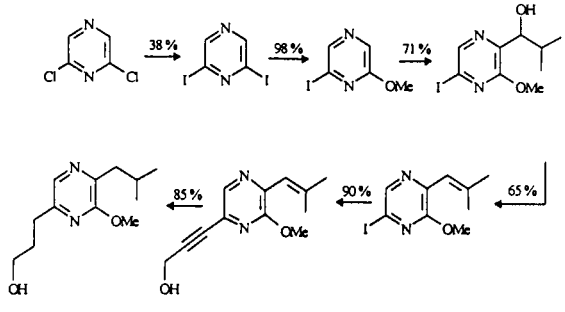
Scheme X

To prepare the target compound **8** it was necessary to reduce both the double and triple bonds. This was done with palladium as catalyst in good yield (Scheme XI).



Scheme XI

In summary, the complete route to **8** was as follows (Scheme XII).



Scheme XII

EXPERIMENTAL

Melting points were determined on a Kofler hot stage and are uncorrected. The ^1H nmr spectra were recorded in deuteriochloroform with tetramethylsilane as the internal standard or in deuterated dimethyl sulfoxide with hexamethyldisiloxane as the internal standard on a Varian EM 360 L or a Bruker AC 200 instrument. Microanalyses were performed on a Carlo Erba CHNOS 1106 apparatus. Tetrahydrofuran was distilled from benzophenone and sodium and used immediately. Water content of the solvent was estimated by the modified :Karl-Fischer method (THF less than 50 ppm water). Metalations were performed under an argon atmosphere whose water content was regularly checked. Reagents were handled with syringues through septa.

Metalation Reactions General Procedure:

A solution of *n*-butyllithium in hexane (x ml, n_1 mmole) was added to cold (-10°), stirred anhydrous THF (40 ml) under dry argon. The mixture was cooled to -30° and 2,2,6,6-tetramethylpiperidine (y ml, n_2 mmole) was added, the solution was warmed to 0° then cooled to -70°, the pyrazine to metalate (z g, n_3 mmole) was dissolved in 5 ml of THF and added to this mixture which was stirred for 2 hours at -70°.

The electrophile isobutanal (n_4 mmole) was added and stirring was continued for 2 hours at -70°. Hydrolysis was carried out at -70° using a mixture of 35% hydrochloric acid (1 ml), ethanol (4 ml) and THF (5 ml). The mixture was gently warmed to room temperature, neutralized with a saturated hydrogenocarbonate solution and evaporated nearly to dryness. The oily residue was extracted three times with dichloromethane (10 ml). The organic extract was dried with anhydrous magnesium sulphate and evaporated. The crude product was purified by column chromatography on silica gel using various eluents.

2,6-Dichloro-3-(1-hydroxyisobutyl)pyrazine (**10**).

Metalation was by the general procedure with *n*-butyllithium in 2.5 *M* hexane (3.76 ml, 9.41 mmoles), 2,2,6,6-tetramethylpiperidine (1.7 ml, 10.1 mmoles), 2,6-dichloropyrazine (1 g, 6.7 mmoles) and isobutanal (6.1 ml, 67 mmoles). The eluent was dichloromethane. A yellow oil was obtained, 0.71 g (49%); ^1H nmr (deuteriochloroform): δ 0.7 (d, 3H, CH_3, J = 7 Hz), 1.03 (d, 3H, CH_3, J = 7 Hz), 2.1 [m, 1H, C*H*$(CH_3)_2$], 3.3 (m, 1H, OH), 4.9 (m, 1H, (C*H*OH), 8.52 (s, 1H, H_5).
Anal. Calcd for $C_8H_{10}Cl_2N_2O$ (M= 220): C, 43.46; N, 12.73; H, 4.54. Found: C, 43.5; N, 12.8; H, 4.6.

2-Methoxy-6-chloro-3-(1-hydroxyisobutyl)pyrazine (**12**) and 2-Chloro-6-methoxy-3-(1-hydroxyisobutyl)pyrazine (**13**).

a) Metalation with Lithium 2,2,6,6-Tetramethylpiperidide.

The reaction was carried out by the general procedure with 2.3 *M* *n*-butyllithium in hexane 0.73 ml, 1.7 mmoles), 2,2,6,6-tetramethylpiperidine (0.3 ml, 1.77 mmoles), 2-chloro-6-methoxypyrazine (0.111 g, 0.77 mmole), and isobutanal (0.73 ml, 8 mmoles). The eluent was dichloromethane:ethyl acetate (90/10). A pale yellow oil was obtained, 0.096 g (57%) containing 85% of **12** and 15% of **13**, ^1H nmr (deuteriochloroform): **12**, δ 0.8 (d, 3H, CH_3, J = 7 Hz), 1.0 (d, 3H, CH_3, J = 7 Hz), 2.08 [m, 1H, C*H*$(CH_3)_2$], 3.59 (d, 1H, OH, J = 8 Hz), 4.00 (s, 3H, OCH_3), 4.71 (m, 1H, C*H*OH), 8.09 (s, 1H, H_5), ^1H nmr: **13** δ 0.8 (d, 3H, CH_3, J = 7 Hz), 1.0 (d, 3H, CH_3, J = 7 Hz), 1.9 [m, 1H, C*H*$(CH_3)_2$], 3.4 (d, 1H, OH, J = 8 Hz), 3.98 (s, 3H, OCH_3), 4.8 (m, 1H, (C*H*OH), 8.12 (s, 1H, H_5).
Anal. Calcd for $C_9H_{13}ClN_2O_2$ (M= 216.5): C, 49 88; N, 12 93; H, 6 00. Found: C, 49.9; N, 12.6; H, 6.1.

b) Metalation with Lithium Diisopropylamide.

The reaction was carried out by the general procedure with 2.3 *M* *n*-butyllithium in hexane (0.73 ml, 1.7 mmoles), diisopropylamine (0.22 ml, 1.6 mmoles), 2-chloro-6-methoxypyrazine (0.10 g, 0.7 mmole), and isobutanal (0.63 ml, 7 mmoles). A yellow oil was obtained, 0.136 g (90%) containing 87% of **12** and 13%, of **13**.

Methyl 3-(6-Chloro-2-pyrazinyl)acrylate (**14**).

In a sealed tube were added 2,6-dichloropyrazine (0.112 g, 0.75 mmole), methyl acrylate (0.27 ml, 3 mmoles), palladium(II) acetate (0.05 g, 0.22 mmole) and triethylamine (0.5 ml). The mixture was heated 16 hours at 115°. The filtered solution was diluted with chloroform (40 ml), washed with a solution of 10% hydrochloric acid (10 ml) and twice with water (20 ml). The aqueous extracts were extracted with chloroform (30 ml). The chloroform extracts were dried over anhydrous magnesium sulphate and the solvent was evaporated under vacuum. The crude product was purified by silica gel column chromatography. The eluent was dichloromethane:ethyl acetate (90/10). A pale yellow oil was obtained, 0.037 g (25%) which was characterized by its ^1H nmr spectrum; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.73 (s, 3H, OCH_3), 6.90 (d, 1H, CH, J = 16 Hz), 7.70 (d, 1H, CH, J = 16 Hz), 8.80 (s, 1H, pyrazine H), 8.95 (s, 1H, pyrazine H).

3-(6-Chloro-2-pyrazinyl)propynol (**15**).

a) With Tetrakis(triphenylphosphine)palladium.

A mixture of 2,6-dichloropyrazine (0.200 g, 1.34 mmoles), propargyl alcohol (0.08 ml, 1.34 mmoles), potassium acetate (0.131 g, 1.34 mmoles) and triethylamine (10 ml) was degassed with argon during 1 hour after which tetrakis(triphenylphosphine)palladium (0.17 g, 0.134 mmole) was added. The solution was refluxed during 2 hours. Then 20 ml of water was added and the mixture extracted four times with ether (10 ml). After drying with anhydrous magnesium sulphate and elimination of solvent, the crude product was purified by silica gel column chromatography. The eluent was dichloromethane: ethyl acetate (80/20). A yellow powder was obtained, 0.022 g (10%), mp 96°; ^1H nmr (deuteriochloroform): δ 3.15 (m, 1H, OH), 4.50 (s, 2H, CH_2), 8.5 (m, 2H, H_3, H_5).
Anal. Calcd. for $C_7H_5ClN_2O$ (M= 168.5): C, 49.85; N, 16.62; H, 2.97. Found: C, 49.6; N, 16.9; H, 2.9

b) With Bis(triphenylphosphine)palladium(II) Chloride/ Copper(I) Iodide.

Copper (I) iodide (0.058 g, 0.3 mmole) was dissolved in triethylamine (5 ml) with slight heating. After cooling, three drops of propargyl alcohol was added and the mixture was stirred during 10 minutes. Then bis(triphenylphosphine)palladium(II) chloride (0.07 g, 0.1 mmole) was added and stirred during 10 minutes after which 2-6-dichloropyrazine (0.3 g, 2.01 mmoles) dissolved in triethylamine (3 ml) and propargyl alcohol (0.12 g, 2.01 mmoles) were added. The mixture was refluxed during 2 hours. After evaporation of the solvent, water (20 ml) was added and the mixture extracted three times with dichloromethane (20 ml).

The extracts were dried with magnesium sulphate and the crude product was purified by silica gel column chromatography. The eluent was dichloromethane:ethyl acetate (80/20). A yellow powder was obtained; 0.129 g (38%). Physical characteristics were as above.

2,6-Diiodopyrazine (**16**).

A mixture of 2,6-dichloropyrazine (2.5 g, 16.8 mmoles), *p*-toluenesulfonic acid (6.38 g, 33.6 mmoles), sodium iodide (20 g, 133.3 mmoles), 15-crown-5 (2 ml) and sulfolane (40 ml) was heated at 150° during 2 hours. After cooling, 100 ml of water was added. The mixture was made neutral with a saturated solution of hydrogenocarbonate and was made lighter in color with a saturated solution of sodium thiosulfate. The resulting solution was extracted five times with ether (40 ml). The ether extracts were dried with anhydrous magnesium sulphate and evaporated. The 2,6-diiodopyrazine was precipitated with 10 ml of water, filtered and washed with water. A pale yellow powder was obtained, 2.12 g (38%). Physical characteristics are those in the literature [15].

2-Iodo-6-methoxypyrazine (**17**).

A solution of sodium methylate was prepared with sodium (0.208 g, 9.04 g-atoms) in methanol (50 ml). After cooling, 2,6-diiodopyrazine (3 g, 9.04 mmoles) was added and stirred 15 hours at room temperature. The solvent was evaporated and the residue was treated with water (15 ml). The mixture was extracted three times with dichloromethane (20 ml) after drying with anhydrous magnesium sulphate and evaporation of the solvent, a golden yellow powder was obtained, 2.09 g (98%), mp < 50°; ^{1}H nmr (deuteriochloroform): δ 3.95 (s, 3H, OCH_3), 8.10 (s, 1H, H_5), 8.35 (s, 1H, H_3).

Anal. Calcd. for $C_5H_5IN_2O$ (M = 236): C, 25.42; N, 11.86; H, 2.12. Found: C, 25.7; N, 11.5; H, 1.9.

2-Iodo-6-methoxy-5-(1-hydroxyisobutyl)pyrazine (**18**).

Metalation was accomplished by the general procedure with 2.5 *M* *n*-butyllithium in hexane (3.73 ml, 9.32 mmoles), diisopropylamine (1.36 ml, 9.75 mmoles), 2-iodo-6-methoxyprazine (1.00 g, 4.24 mmoles), and isobutanal (2.4 ml, 26.5 mmoles). A colourless oil was obtained 0.927 g (71%); ^{1}H nmr (deuteriochloroform): δ 0.85 (d, 3H, CH_3, J = 7 Hz), 1.05 (d, 3H, CH_3, J = 7 Hz), 2.05 [m, 1H, C*H*$(CH_3)_2$], 3.6 (m, 1H, OH), 3.95 (s, 3H, OCH_3), 4.65 (m, 1H, C*H*OH), 8.30 (s, 1H, H_3).

Anal Calcd. for $C_9H_{13}IN_2O_2$ (M = 308): C, 35.06, N, 9.09; H, 4.22. Found: C, 35.0; N, 8.9; H, 4.3.

Reduction Attempts with a Benzylic Type Alcohol.

The reduction of 2,6-dichloro-3-(1-hydroxyisobutyl)pyrazine (**10**) was attempted unsuccessfully with sodium borohydride and aluminum chloride in THF as with triethylsilane and trifluoroacetic acid. The reduction of 2-iodo-6-methoxy-5-(1-hydroxyisobutyl)pyrazine (**18**) was also attempted unsuccessfully with trimethylchlorosilane, sodium iodide in acetonitrile followed by zinc powder and acid acetic in the same solvent. With 2-chloro-3-(1-hydroxybenzyl) pyrazine were also tested: sodium borohydride in trifluoroacetic acid and a mixture of cyclohexene, aluminum chloride and 5% palladium on carbon. In all cases the reductions failed.

3-(6-Methoxy-2-pyrazinyl)propynol (**19**).

The same procedure described for **15** was used with the following quantities: Copper(I) iodide (0.212 g, 0.06 mmole), bis(triphenyl phosphine)palladium(II) chloride (0.022 g, 0.03 mmole), 2-iodo-6-methoxypyrazine (0.1 g, 0.42 mmole), propargyl alcohol (0.15 ml, 2.58 mmoles). The eluent was dichloromethane: ethyl acetate (92/8). A sublimation was necessary to afford a pure product as a white powder, 0.056 g (82%), mp 116°; ^{1}H nmr (deuteriochloroform): δ 3.3 (m, 1H, OH), 4.00 (s, 3H, OCH_3), 4.6 (s, 2H,CH_2OH), 8.2 (m, 2H, H3, H_5).

Anal. Calcd. for $C_8H_8N_2O_2$ (M = 164): C, 58.54; N, 17.07; H, 4.88. Found: C, 58.8; N, 16.7; H, 4.9.

3-[6-Methoxy-5-(1-hydroxyisobutyl)pyrazinyl]propynol (**20**).

The same procedure described for **15** was employed with the following quantities: Copper(I) iodide (0.012 g, 0.06 mmole), bis(triphenylphosphine)palladium(II) chloride (0.022 g, 0.03 mmole), 2-iodo-6-methoxy-5-(1-hydroxyisobutyl)pyrazine (0.128 g, 0.42 mmole), and propargyl alcohol (0.1 ml, 1.72 mmoles). The eluent was a mixture of cyclohexane and dichloromethane (50/50). A colourless oil was obtained, 0.069 g (70%); ^{1}H nmr (deuteriochloroform): δ 0.75 (d, 3H, CH_3, J = 7 Hz), 1.05 (d, 3H, CH_3, J = 7 Hz), 2.1 (m, 1H, C*H*$(CH_3)_2$), 3.8 (m, 1H, OH), 3.95 (s, 3H, OCH_3), 4.45 (s, 2H, CH_2OH), 4.70 [m, 1H, -CHO*H*$(CH_3)_2$], 8.1 (s, 1H, H_3).
Anal. Calcd. for $C_{12}H_{16}N_2O_3$ (M = 236): C, 61.02; N, 11.86; H, 6.78. Found: C, 61 .4; N, 11.5; H, 6.8.

2-Methoxy-3-(2-methyl-1-propenyl)-6-iodopyrazine (**21**).

In a 100 ml flask fitted with a Dean Stark apparatus were introduced 2-iodo-6-methoxy-5-(1-hydroxyisobutyl)pyrazine (**18**) (0.60 g, 1.95 mmoles), *p*-toluenesulphonic acid (1.112 g, 5.85 mmoles) and 40 ml of toluene. The mixture was refluxed for 6 hours. After cooling the toluene solution was washed three times with 30 ml of water, then the toluene solution was dried with anhydrous magnesium sulphate and purified by silica gel chromatography with dichloromethane:cyclohexane (50/50) as eluent. A yellow oil was obtained, 0.37 g (65%); ^{1}H nmr (deuteriochloroform): δ 1.95 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 4.00 (s, 3H, OCH_3), 6.4 [s, 1H, C*H*=C$(CH_3)_2$], 8.35 (s, 1H, H_5).

Anal. Calcd. for $C_9H_{11}IN_2O$ (M = 290): C, 37.24; N, 9.66; H, 3.79. Found: C, 37.4; N, 9.5; H, 3.5.

2-Methoxy-3-(2-methyl-1-propenyl)-6-(3-hydroxypropynyl) pyrazine (**22**).

The same procedure as for **15** was used with the following quantities: Copper(I) iodide (0.034 g, 0.018 mmole), bis-(triphenylphosphine)palladium(II) chloride (0.062 g, 0.09 mmole), 2-Methoxy-3-(2-methyl-1-propenyl)-6-iodopyrazine (0.344 g, 1.19 mmoles), and propargyl alcohol (0.35 ml, 6.02 mmoles). The eluent was a mixture of dichloromethane:ethyl acetate (3/1). A yellow powder was obtained, 0.233 g (90%), mp 95°; ^{1}H nmr (deuteriochloroform): δ 1.90 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 2.50 (m, 1H, OH), 3.90 (s, 3H, OCH_3), 4.45 (s, 2H, CH_2OH), 6.35 [d, 1H, C*H*=C$(CH_3)_2$], 8.15 (s, 1H, H_5).

Anal. Calcd. for $C_{12}H_{14}N_2O_2$ (M = 218): C, 66.06; N, 12.44; H, 6.42. Found: C, 65.8; N, 12.1; H, 6.3.

2-Methoxy-3-(1-isobutyl)-6-(3-hydroxypropyl)pyrazine (**8**).

In a classical apparatus for hydrogenation at atmospheric pressure was added product **22** (0.054 g, 0.25 mmole) and 10% palladium on charcoal (0.011 g, 0.01 mmole) with dry ethanol (7

ml). After absorption of the required hydrogen quantity (~ 16.7 ml) the solution was filtrated on celite. In some cases it was necessary to add a small amount of catalyst after 1 hour to complete the reduction. A yellow oil was obtained; 0.048 g (85%).

Physical characteristics are identical to those in the literature.

Anal Calcd. for $C_{12}H_{20}N_2O_2$ (M = 224): C, 64.29; N, 12.50; H, 8.93. Found: C, 64.3; N, 12.4; H, 9.3.

REFERENCES AND NOTES

[1] A. Ohta, Y. Aoyagi, Y. Kurihara, K. Yuasa. and M. Shimazaki, *Heterocycles*, **26**, 3181 (1987).

[2] A Ohta, Y. Aoyagi, Y. Kurihara, A. Kojima, K. Yuasa, and M. Shimazaki, *Heterocycles*, **27**, 437 (1988).

[3] A. Turck, D. Trohay, L. Mojovic, N. Plé and G. Quéguiner, *J. Organometal. Chem.*, **412**, 301 (1991).

[4] A. Turck, N. Plé and G. Quéguiner, *Heterocycles*, **37**, 2149 (1994).

[5] D. E. Ames and M. I.. Brohi. *J. Chem. Soc., Perkin Trans. I*, 1384 (1980).

[6] D. E. Ames, D. Bull and C. Takundwa, *Synthesis*, 364 (1981).

[7] Y. Akita, A. Inoue and A. Ohta, *Chem. Pharm. Bull.*, **34**, 1447 (1986).

[8] E. C. Taylor and P. S. Ray, *J. Org Chem.*, **52**, 3997 (1987).

[9] Y. Akita, H. Kanekawa, T. Kawasaki, I. Shiratori and A. Ohta, *J. Heterocyclic Chem.*, **25**, 975 (1988).

[10] M. J. Chapdelaine, P. J. Warwick and A. Shaw, *J. Org. Chem.*, **54**, 1218 (1989).

[11] D. E. Ames and D. Bull, *Tetrahedron*, **38**, 383 (1982).

[12] T. Sakamoto, Y. Koudo and H. Yamanaka, *Chem. Pharm. Bull.*, **30**, 2410 (1982).

[13] J. Solberg and K. Undheim, *Acta Chem. Scand., Ser. B*, **41**, 712 (1987).

[14] A. Wada, H. Yasuda and S. Kanatomo, *Synthesis*, 771 (1988).

[15] L. Street, *J. Med. Chem.*, **35**, 295 (1992).