Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. H:EA refers to hexanes:ethyl acetate solvent mixtures for TLC and silica gel flash chromatography (SGC). The purity of all title compounds was determined to be >95% by 300-MHz proton NMR and/or NMR, melting point, and TLC comparison with authentic samples.

Representative Procedure. Benzoquinone (4.80 g, 44.4 mmol) and freshly distilled butyraldehyde (20 mL, 346.7 mmol) were dissolved in dry benzene (240 mL) and were degassed with nitrogen for 15 min. The solution was irradiated with a high-pressure Hg-vapor lamp with a Pyrex filter for 5 days. The solution was concentrated in vacuo and the residue was purified by SGC using 6:1 H:EA to afford 6.55 g (82% yield) of **1a** as pale yellow crystals.

1-(2,5-Dihydroxyphenyl)-1-butanone (1a): TLC (H:EA = 4:1) R_f = 0.42; mp 94–96 °C (H–benzene) (lit.[7] mp 96 °C).

(2,5-Dihydroxyphenyl)(phenyl)methanone (1b): TLC (H:EA = 4:1) R_f = 0.38; mp 121–123 °C (H–benzene) (lit.[9] mp 122–124 °C).

1-(2,5-Dihydroxyphenyl)-2-buten-1-one (1c): NMR ($CDCl_3$) δ 1.97 (d, 3 H/2, J = 7 Hz), 2.02 (d, 3 H/2, J = 7 Hz), 6.01–6.07 (m, 1 H), 6.74–6.78 (m, 1 H), 6.87–7.05 (m, 2 H), 7.12–7.26 (m, 1 H), 12.27 (s, 1 H); IR (CH_2Cl_2) 1730, 1650, 15.90 cm^{-1}; HRMS m/z for $C_{10}H_{10}O_3$ calcd 178.062 99, found 178.062 73; TLC (H:EA = 4:1) R_f = 0.31; mp 114–116 °C ($CHCl_3$–EA).

3-Phenyl-1-(2,5-dihydroxyphenyl)-2-propen-1-one (1d): TLC (H:EA = 4:1) R_f = 0.32; mp 168–170 °C (H–benzene) (lit.[4] mp 170 °C).

(2,5-Dihydroxyphenyl)(2-methoxyphenyl)methanone (1e): NMR ($CDCl_3$) δ 3.80 (s, 3 H), 6.80 (s, 1 H), 6.92–7.09 (m, 4 H), 7.27–7.30 (m, 1 H) 7.49 (t, 1 H, J = Hz), 11.75 (s, 1 H); IR (CH_2Cl_2) 1610 cm^{-1}; HRMS m/z for $C_{14}H_{12}O_4$ calcd 244.073 56, found 244.073 12; TLC (H:EA = 4:1) R_f = 0.25; mp 145–148 °C (H–$CHCl_3$).

3-(2-Furanyl)-1-(2,5-dihydroxyphenyl)-2-propen-1-one (1f): NMR ($CDCl_3$) δ 5.65 (s, 1 H), 6.50–6.51 (m, 2 H), 6.69 (d, 1 H, J = 3 Hz), 6.73–6.78 (m, 2 H), 6.94–6.98 (m, 2 H), 7.53–7.57 (m, 2 H); IR (CH_2Cl_2) 1720, 1630 cm^{-1}; HRMS m/z for $C_{13}H_{10}O_4$ calcd 230.057 91, calcd 230.057 63; TLC (H:EA = 4:1) R_F = 0.48; MP 134–136 °C ($CHCl_3$–EA).

(1,4-Dihydroxy-2-naphthyl)-1-butanone (4a): TLC (H:EA = 4:1) R_f = 0.50; mp 141–143 °C (H–benzene) (lit.[8] mp 143 °C).

(1,4-Dihydroxy-2-naphthyl)phenylmethanone (4b): NMR ($CDCl_3$) δ 7.41–7.53 (m, 3 H), 7.56–7.71 (m, 4 H), 8.11 (d, J = 4 Hz, 1 H), 8.50 (d, J = 4 Hz, 1 H), 13.54 (s, 1 H); IR ($CHCl_3$) 1600 cm^{-1}; MS CI (NH_3) 282 ($M^+ + NH_4$); TLC (H:EA = 4:1) R_f = 0.50; mp 124–126 °C (H–$CHCl_3$).

(1,4-Dihydroxy-2-naphthyl)-2-buten-1-one (4c): NMR ($CDCl_3$) δ 2.04 (d, 3 H, J = 7 Hz), 7.01 (d, 1 H, J = 6 Hz), 7.08 (s, 1 H), 7.20–7.23 (m, 1 H), 7.57 (t, 1 H, J = 5 Hz), 7.68 (t, 1 H, J = 5 Hz), 8.14 (d, 1 H, J = 5 Hz), 8.47 (d, 1 H, J = 5 Hz), 14.29 (s, 1 H); IR (CH_2Cl_2) 1640, 1590 cm^{-1}; HRMS m/z for $C_{14}H_{12}O_3$ calcd 228.078 64, found 228.078 54; TLC (H:EA = 4:1) R_f = 0.33; mp 183–186 °C ($CHCl_3$–EA).

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Registry No. **1a**, 4693-16-7; **1b**, 2050-37-5; **1c**, 140660-42-0; **1d**, 19312-13-1; **1e**, 140660-43-1; **1f**, 140660-44-2; **2**, 106-51-4; **3**, 130-15-4; **4a**, 72827-02-2; **4b**, 94797-68-9; **4c**, 140660-45-3; $CH_3(CH_2)_2CHO$, 123-72-8; PhCHO, 100-52-7; $CH_3CH{=}CHCHO$, 4170-30-3; $PhCH{=}CHCHO$, 104-55-2; o-$CH_3OC_6H_4CHO$, 135-02-4; 3-(2-furyl)-2-propenal, 623-30-3.

Supplementary Material Available: Proton NMR data for compounds **1c**, **1e**, **1f**, **4b**, and **4c** (5 pages). Ordering information is given on any current masthead page.

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A General and Convenient Synthesis of 3-Aminopyridazines

Jean-Marie Sitamze, Martine Schmitt, and Camille-Georges Wermuth*

Laboratoire de Pharmacochimie Moléculaire, UPR 421 du C.N.R.S., 5, rue Blaise Pascal, 67000 Strasbourg, France

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During our investigations on psychotropic pyridazine derivatives,[1-4] we needed to prepare 3-aminopyridazines bearing various substituents on the pyridazine ring. Usually, such compounds are prepared by ammonolysis of the corresponding 3-halopyridazines[5] (Scheme I). Depending on the substituents present on the pyridazine ring, this reaction proceeds with extremely variable yields, despite vigorous experimental conditions (autoclave, 100–200 °C, copper catalysts).

The replacement of the halogen atom by other leaving groups was also studied. Thus, Gregory and co-workers prepared 3-amino-6-methylpyridazines by reacting ammonia with the 3-methylthio derivative.[6] After 3 days at 150 °C, the yield was only 18%.

Nucleophilic displacement of 3-alkoxy derivatives is even more difficult.[7] However, 3-mesylated or 3-tosylated pyridazines react with ammonia to give products in yields similar to that observed from 3-halopyridazines.[6,8]

Conversely, the nucleophilic displacement of 3-halopyridazine by means of reagents other than ammonia was also studied (Scheme II). Examples are given by the action of urea on 3-chloro-4-phenyl-6-methylpyridazine[9] and of potassium thiocyanide on 4-bromo-3,5,6-triphenylpyridazine in ethanol, followed by the hydrolysis of the intermediate thiourethane. However, the most convenient method remains the nucleophilic displacement by hydrazine, followed by hydrogenolysis of the initially obtained 3-hydrazinopyridazine.[2,10] This preparation presents the inconvenience of decreasing yields when practiced on samples exceeding 2 g of 3-hydrazinopyridazine.

In the search for a general method giving satisfactory yields and easily applicable on a preparative scale, we became interested in the hydrogenolysis of 3-hydrazinopyridazines by means of nickel–aluminum alloy in alkaline medium which we adapted from Keefer and Lunn.[11] To our knowledge, this reduction procedure, starting from 3-hydrazinopyridazine has never been applied to the production of 3-aminopyridazines. A possible reason may be the observation made by Lunn[12] that in simple pyridazines, nickel–aluminum alloy reduction destroys the

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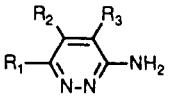
0022-3263/92/1957-3257$03.00/0

Table I. Yields and ^{1}H-NMR Data of 3-Aminopyridazines

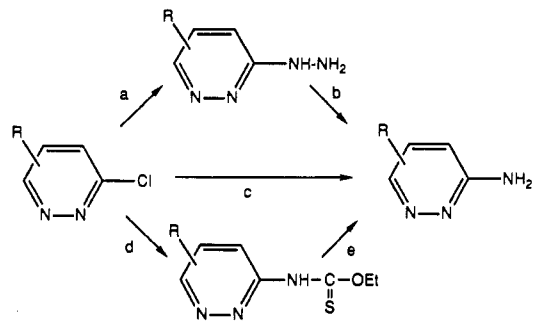


substrates	R_1	R_2	R_3	yield, %	mp, °C (solvent)	^{1}H NMR (200 Hz), $CDCl_3$
1	$CH_3OC_6H_4$	H	H	84	171.5 (EtOH)	3.69 (s, 3 H), 4.7 (br s, NH_2), 6.81 (d, 1 H, J = 9.17 Hz), 6.98 (d, 2 H, J = 8.88 Hz), 7.58 (d, 1 H, J = 9.17 Hz), 7.90 (d, 2 H, J = 8.88 Hz)
2	C_6H_5	H	CH_3	76	130 (EtOH)	2.27 (s, 3 H), 5.14 (br s, NH_2), 7.41–7.53 (m, 4 H), 7.93–7.98 (m, 2 H)
3	CH_3	C_6H_5	H	81	169 (EtOH)	2.50 (s, 3 H), 5.20 (br s, NH_2), 6.74 (s, 1 H), 7.26–7.51 (m, 5 H)
4	C_6H_5	H	C_2H_5	84	149.5 (EtOH)	1.37 (t, 3 H), 2.59 (q, 2 H), 5.26 (br s, NH_2), 7.38–7.53 (m, 4 H), 7.94–7.99 (m, 2 H)
5	C_6H_5	CH_3	H	81	152 (EtOH)	2.26 (s, 3 H), 5.10 (br s, NH_2), 6.75 (s, 1 H), 7.42–7.51 (m, 5 H)
6	C_6H_5	$CH_3CH_2CH_2$	H	81	137 (EtOH)	0.65 (t, 3 H), 1.44–1.56 (m, 2 H), 2.54 (t, 2 H), 4.74 (br s, NH_2), 6.65 (s, 1 H), 7.41–7.51 (m, 5 H)
7	C_6H_5	H	$(CH_3)_2CH$	82	154 (EtOH)	1.35 (d, 6 H), 2.77–2.91 (m, 1 H), 5.15 (br s, NH_2), 7.36–7.53 (m, 4 H), 7.92–7.98 (m, 2 H)
8	H	C_6H_5	H	70	203 (H_2O	6.91 (d, 1 H, J = 1.87 Hz), 4.87 (br s, NH_2), 7.47–7.65 (m, 5 H), 8.89 (d, 1 H, J = 1.87 Hz)
9	C_6H_5	H	$C_6H_5CH_2$	84	210 (EtOH)	3.96 (s, 2 H), 5.41 (br s, NH_2), 7.20–7.50 (m, 9 H), 7.88–7.93 (m, 2 H)
10	C_6H_5	H	$C_6H_5CH_2CH_2$	83	158 (EtOH)	2.79–2.87 (t, 2 H), 3.01–3.08 (t, 2 H), 4.83 (br s, Nh_2), 7.18–7.51 (m, 9 H), 7.88–7.92 (m, 2 H)
11	C_6H_5	H	$CH_3C_6H_4CH_2$	85	227.5 (EtOH)	2.36 (s, 3 H), 3.98 (s, 2 H), 4.96 (br s, NH_2), 7.06–7.26 (m, 4 H), 7.47–7.51 (m, 4 H), 7.92–7.96 (m, 2 H)

Scheme I

X = Cl, Br, -SCH_3, -OCH_3, -SO_2-CH_3, -SO_2-C_6H_4-CH_3

Scheme II[a]



[a] (a) N_2H_4, *n*-BuOH, 100 °C, 12 h; (b) H_2, Ni, MeOH; (c) H_2NCONH_2, 190 °C, 40 h; (d) KSCN, EtOH, 80 °C, 15 h; (e) EtOH, H_2SO_4 50%, reflux 10 h.

pyridazine ring, splitting the N–N bond and leading to saturated 1,4-diamines. We observed that in 3-hydrazinopyridazines this ring cleavage did not occur and that only the exocyclic N–N bond was reduced, yielding regularly the expected 3-aminopyridazines in yields ranging from 70 to 85% (Table I).

Experimental Section

^{1}H-NMR spectra were recorded with a Brucker AS 200 spectrometer. Tetramethylsilane served as an internal standard. Nickel–aluminum alloy was purchased from Prolabo. All starting materials were prepared in our laboratory, following our previously described procedures.[1-4]

Typical Procedure for the Preparation of 3-Aminopyridazines. To a solution of 10 g (0.046 mol) of 3-hydrazino-6-(*p*-methoxyphenyl)pyridazine in 400 mL of methanol and 400 mL of 1 M potassium hydroxide, 30 g of nickel–aluminum alloy were progressively added in small quantities. The solution was stirred vigorously at room temperature during addition. After 2 h, the solution was filtered over diatomaceous earth and the methanol evaporated. The residue was dissolved in water and extracted with ethyl acetate. After removal of the organic solvent under reduced pressure, 7.81 g (84%) of 3-amino-6-(*p*-methoxyphenyl)pyridazine was obtained. For synthetic purposes, further purification of this intermediate was not necessary. The other 3-aminopyridazines (Table I) were prepared using the same general method.

Caution. The reaction of nickel–aluminum alloy with potassium hydroxide solutions produces copious amounts of flammable hydrogen, and so the reaction should be done in a chemical fume hood. In addition the spent nickel which is removed by filtration is potentially pyrophoric and should be allowed to dry on a metal tray away from flammable solvents for 24 h before disposal (see ref 12).

Registry No. 1, 18772-76-4; 1 amine, 4776-87-8; 2, 32723-48-1; 2 amine, 81819-90-1; 3, 140149-38-8; 3 amine, 105537-98-2; 4, 140149-39-9; 4 amine, 140149-40-2; 5, 140149-41-3; 5 amine, 105537-96-0; 6, 140149-42-4; 6 amine, 140149-43-5; 7, 140149-44-6; 7 amine, 140149-45-7; 8, 100079-09-2; 8 amine, 105537-97-1; 9, 64657-84-7; 9 amine, 140149-46-8; 10, 140149-47-9; 10 amine, 140149-48-0; 11, 140149-49-1; 11 amine, 140149-50-4; Al, 7429-90-5; Ni, 7440-02-0.

Supplementary Material Available: Data resulting from elemental analysis of 1–11 (1 page). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.