A Revision of the Alcoholysis and Alkanethiolysis of 3-Amino-6-chloropyridazine

Bert U. W. Maes [a], Guy L. F. Lemière [a],* Roger Dommisse [a] and Achiel Haemers [b]

[a] Department of Chemistry, University of Antwerp (RUCA), Groenenborgerlaan 171, B-2020 Antwerpen, Belgium
[b] Department of Medicinal Chemistry, University of Antwerp (UIA), Universiteitsplein 1, B-2610 Antwerpen, Belgium

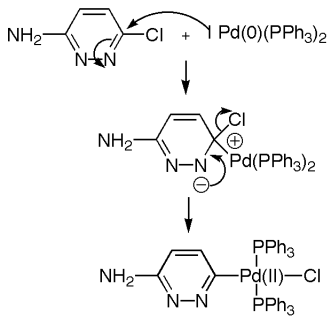
Received March 28, 2001

The synthesis of 3-amino-6-alkoxy- and 3-amino-6-alkylthiopyridazines *via* nucleophilic aromatic substitution on 3-amino-6-chloropyridazine is described. In contrast to literature reports, no pressure tube is required to perform these reactions.

J. Heterocyclic Chem., **38**, 1215 (2001).

In the literature it is well documented that the amino group of 3-amino-6-chloropyridazine (**1**) deactivates the C-6 position for nucleophilic attack and extreme reaction conditions are reported to perform nucleophilic aromatic substitution reactions on this skeleton [1]. In the standard literature procedure for the alcoholysis (boiling point of alcohol < 140 °C) and alkanethiolysis of **1** an autoclave is used as the reaction vessel. Recently, we described successful Suzuki and Stille arylations on 3-amino-6-chloropyridazine (**1**) under reflux [2]. Since the mechanism of oxidative addition can be explained as a nucleophilic attack of $Pd(0)(PPh_3)_2$ on **1** [3] (Scheme 1) we decided to revise the alcoholysis and alkanethiolysis on this skeleton under reflux. Moreover, a more practical approach for the synthesis of 3-amino-6-alkoxy- and 3-amino-6-alkylthiopyridazines is desirable since these compounds are valuable starting materials for the preparation of biologically active imidazo[1,2-*b*]pyridazines [1].

Scheme 1



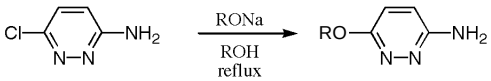
Oxidative addition of 3-amino-6-chloropyridazine to $Pd(0)(PPh_3)_2$

In 1958 Clark *et al.*, described the synthesis of 3-amino-6-methoxypyridazine (**2**) *via* methanolysis of **1** [4]. They heated **1** and sodium methanolate in methanol in an autoclave at 120 °C for 20 hours. After working up the reaction mixture only 15% of **2** was obtained. Clark and co-workers also reported that attempts to perform this reaction under reflux were unsuccessful; no 3-amino-6-methoxypyridazine (**2**) could be obtained in this manner. The resistance of **1** towards nucleophilic attack of alkoxides under reflux has also been reported by other authors [5-7]. In 1962 Horie *et al.*, published a general protocol for the synthesis of 6-alkoxy-3-aminopyridazines from **1** [8]. Alcoholysis with alcohols boiling lower than 140 °C were performed in an autoclave at 120-130 °C for 6-10 hours. Hitherto this procedure is the standard protocol for the synthesis of 6-alkoxy-3-aminopyridazines from **1** [9-18]. In the same article Horie *et al.*, also describe a general protocol for the alkanethiolysis of **1**. 3-Amino-6-chloropyridazine (**1**) and sodium alkanethiolates are heated in dioxane at 120-140 °C for 8 hours. Also in this case the use of an autoclave has become the standard procedure [19-25].

In Table 1 and 2 our results on alcoholysis and alkanethiolysis of **1** under reflux are summarized. These results clearly show that there is no need to use an autoclave as the reaction vessel. Good results can also be obtained under simple reflux (Table 1 and 2). Moreover, higher yields are obtained under reflux (Table 2) than under pressure. In the literature for the alcoholysis under pressure usually only crude yields are reported, which makes comparison impossible. Only for the synthesis of 3-amino-6-methoxypyridazine (**2**) a yield of 15% for the purified reaction product

Table 1

Synthesis of 6-Alkoxy-3-aminopyridazines *via* Alcoholysis of 3-Amino-6-chloropyridazine



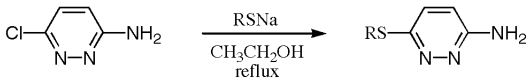
1 **2-4**

R	Reaction product	Yield (%)[a]	Reaction time (h)
CH_3	**2**	89	72
CH_3CH_2	**3**	94	26.5
$CH_3CH_2CH_2$	**4**	81	14

[a] Reaction conditions: **1** (10.80 mmol), RONa (11.96 mmol), ROH (50 mL), reflux (temperature of the oil bath = 20 °C above the reflux temperature of the alcohol).

Table 2

Synthesis of 6-Alkylthio-3-aminopyridazines *via* Alkanethiolysis of 3-Amino-6-chloropyridazine



1 **5-7**

R	Reaction product	Yield (%) [a] atmospheric pressure	Reaction time (h)	Yield (%) pressure (bomb tube)	Reaction time (h)
CH_3	**5**	90	53	79 [19]	12
CH_3CH_2	**6**	99	53	86 [b], [21]	16
$CH_3CH_2CH_2$	**7**	89	53	67 [21]	17

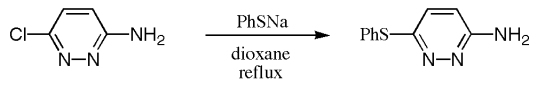
[a] Reaction conditions: **1** (4.86 mmol), RSNa (21.4 mmol), CH_3CH_2OH (20 mL), 98°C (oil bath). [b] crude.

is reported [4]. Generally the reaction times of our reactions under reflux are longer than those reported in the literature under pressure. This is not surprising since our conditions are milder. For the alcoholysis of **1**, as expected, the reaction time decreases with increasing boiling point of the alcohol.

Attempts to expand the alcoholysis and alkanethiolysis towards phenolysis and thiophenolysis under reflux in ethanol were unsuccessful. Even after 4 days of reflux large amounts of starting material remained unconsumed. Replacement of ethanol with the higher boiling dioxane in the synthesis of 3-amino-6-phenylthiopyridazine (**9**) from **1** and sodium phenylthiolate gave an excellent yield (98%) of **9** in 60 hours of reflux (Table 3). However, a similar reaction with the less nucleophilic phenolate was unsuccessful. Only traces of 3-amino-6-phenoxypyridazine (**10**) could be detected with DCI-MS even after 72 hours of reflux.

Table 3

Synthesis of 3-Amino-6-phenythiopyridazine *via* Thiophenolysis of 3-Amino-6-chloropyridazine



1 **9**

Reaction product	Yield (%) [a] atmospheric pressure	Reaction time (h)	Yield (%) pressure (bomb tube)	Reaction time (h)
9	98	60	53,5[21]	18

[a] Reaction conditions: **1** (4.86 mmol), PhSNa (21.4 mmol), dioxane (20 mL), 112 °C (oil bath).

EXPERIMENTAL

NMR spectra were recorded on a Varian Unity 400 spectrometer. For mass-spectrometry analysis, samples were dissolved in CH_3OH containing 0.1% formic acid and diluted to a concentration of approximately 10^{-5} mol/L. 1µL injections were directed to the mass spectrometer at a flow rate of 5µL/minute CH_3OH (0.1% formic acid), using the CapLC HPLC system (Waters, Millford). Product ion spectra and exact mass measurements were performed on a quadrupole-time of flight mass spectrometer (Q-Tof-2, Micromass, Manchester, UK) equipped with a standard electrospray ionisation (ESI) interface. Cone voltage (35V) and capillary voltage (3.3 kV) were optimised on one compound and used for all others. Fragmentation was induced by low energy collisional activation using a collision energy of 30 eV. IR spectra were recorded on a Bruker Vector 22 spectrometer. Melting points were determined on a Büchi B-545 apparatus and are uncorrected. 3-Amino-6-chloropyridazine (**1**) was purchased from Lancaster and Maybridge. Sodium methanethiolate (95%), sodium ethanethiolate (90%), sodium propanethiolate (97%) and sodium thiophenolate (97%) were obtained from Fluka. Methanol, ethanol and propanol (Acros) were dried over magnesium, and dioxane over sodium benzophenone. Flash column chromatography was performed on Kieselgel 60 (Merck), 0.040-0.063 mm.

General Procedure for the Synthesis of **2-4** *via* Alcoholysis

Dry alcohol (50 ml) was added dropwise to sodium (2.75 g, 11.96 mmol). When all the sodium was dissolved, the sodium alcoholate solution was added to 3-amino-6-chloropyridazine (**1**) (1.4 g, 10.80 mmol). The reaction mixture was heated under reflux (temperature of the oil bath = 20 °C above the reflux temperature of the alcohol) under a nitrogen atmosphere until starting material has disappeared as judged by TLC and/or DCI-MS. After cooling the crude reaction mixture was evaporated under reduced pressure to dryness. Water (150 ml) was added. The inorganic phase was extracted with CH_2Cl_2 (7 x 100 ml) and the CH_2Cl_2 evaporated under reduced pressure. The residue was dried under vacuum and purified by flash column chromatography on silica gel. The following compounds were prepared in this manner:

3-Amino-6-methoxypyridazine (**2**).

This compound was prepared with a reaction time of 72 hours; yield: 89%; no column chromatography was required; mp 104 °C (lit 103-105 °C) [4] (white); ir (KBr): ν 3444, 3361, 3304, 3193, 3000, 2965, 1638, 1476, 1427, 1281, 1012, 838, 668, 565, 464 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 6.87 (d, *J* = 9.3 Hz, 1H, H-4 or H-5), 6.85 (d, *J* = 9.3 Hz, 1H, H-4 or H-5), 5.89 (br s, 2H, NH_2), 3.82 ppm (s, 3H, OCH_3); ^{13}C nmr (DMSO-d_6): δ 158.95 (C-3 or C-6), 157.50 (C-3 or C-6), 119.52 (C-4 or C-5), 118.89 (C-4 or C-5), 53.35 ppm (OCH_3); ms (ESI): 111, 83, 54 (100%); hrms (ESI) for $C_5H_8N_3O$ $[M+H]^+$: calcd 126.0667, found 126.0656.

3-Amino-6-ethoxypyridazine (**3**).

This compound was prepared with a reaction time of 26.5 hours; yield: 94%; eluent for flash column chromatography: 1) $CHCl_3$-EtOH (98:2) 2) $CHCl_3$-EtOH (9:1); mp 167 °C (white); ir (KBr): ν 3454, 3419, 3299, 3147, 2980, 2945, 2894, 1639, 1611, 1484, 1461, 1349, 1278, 1179, 1115, 1041, 920, 852, 677, 475

cm^{-1}; ^1H nmr (DMSO-d_6): δ 6.85 (d, *J* = 9.3 Hz, 1H, H-4 or H-5), 6.82 (d, *J* = 9.3 Hz, 1H, H-4 or H-5), 5.84 (br s, 2H, NH_2), 4.28 (q, *J* = 7.0 Hz, 2H, OCH_2), 1.31 ppm (t, *J* = 7.0 Hz, 3H, CH_3); ^{13}C nmr (DMSO-d_6): δ 158.75 (C-3 or C-6), 157.37 (C-3 or C-6), 119.50 (C-4 or C-5), 119.04 (C-4 or C-5), 61.37 (OCH_2), 14.41 ppm (CH_3); ms (ESI): 112, 83, 67 (100%), 54; hrms (ESI) for $C_6H_{10}N_3O$ $[M+H]^+$: calcd 140.0824, found 140.0813.

3-Amino-6-propoxypyridazine (**4**).

This compound was prepared with a reaction time of 14 hours; yield: 81%; eluent for flash column chromatography: EtOAc; mp 75 °C (white); ir (KBr): ν 3397, 3325, 3204, 2967, 2944, 2885, 1634, 1617, 1482, 1462, 1365, 1290, 1185, 1127, 1105, 1061, 971, 842, 562, 478 cm^{-1}; ^1H nmr (DMSO-d_6): δ 6.86 (d, *J* = 9.3 Hz, 1H, H-4 or H-5), 6.82 (d, *J* = 9.3 Hz, 1H, H-4 or H-5), 5.83 (br s, 2H, NH_2), 4.17 (t, *J* = 6.7 Hz, 2H, OCH_2), 1.71 (h, *J* ≈ 7Hz, 2H, CH_2), 0.95 ppm (t, *J* = 7.5 Hz, 3H, CH_3); ^{13}C nmr (DMSO-d_6): δ 158.91 (C-3 or C-6), 157.37 (C-3 or C-6), 119.49 (C-4 or C-5), 119.02 (C-4 or C-5), 67.20 (OCH_2), 21.74 (CH_2), 10.26 ppm (CH_3); ms (ESI): 112 (100%), 83, 67; hrms (ESI) for $C_7H_{12}N_3O$ $[M+H]^+$: calcd 154.0980, found154.0971.

General Procedure for the Synthesis of **5-7** *via* Alkanethiolysis.

A mixture of 3-amino-6-chloropyridazine (**1**) (0.630 g, 4.86 mmol), sodium alkanethiolate (21.4 mmol) and 20 ml ethanol was stirred and heated under reflux (temperature of oil bath = 100 °C) under a nitrogen atmosphere until starting material has disappeared as judged by TLC and/or DCI-MS. After cooling the crude reaction mixture was evaporated under reduced pressure to dryness. Water (200 ml) was added. The inorganic phase was extracted with EtOAc (6 x 100 ml). The combined organic extraction fractions were dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel. The following compounds were prepared in this manner:

3-Amino-6-methylthiopyridazine (**5**).

This compound was prepared with a reaction time of 53 hours; yield: 90%; eluent for flash column chromatography: EtOAc; mp 115 °C (lit 117-118 °C) [19] (white); ir (KBr): ν 3307, 3162, 2922, 1638, 1598, 1454, 1161, 1107, 834, 639, 545, 457 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.20 (d, *J* = 9.3 Hz, 1H, H-5), 6.70 (d, *J* = 9.3 Hz, 1H, H-4), 6.19 (br s, 2H, NH_2), 2.48 ppm (s, 3H, SCH_3); ^{13}C nmr (DMSO-d_6): δ 158.55 (C-3), 150.17 (C-6), 126.97 (C-4 or C-5), 115.02 (C-4 or C-5), 13.10 ppm (SCH_3); ms (ESI): 127, 110, 100 (100%), 79, 49, 47; hrms (ESI) for $C_5H_8N_3S$ $[M+H]^+$: calcd 142.0439, found 142.0435.

3-Amino-6-ethylthiopyridazine (**6**).

This compound was prepared with a reaction time of 53 hours; yield: 99%; eluent for flash column chromatography: $CHCl_3$-EtOH (95:5); mp 46 °C (lit 46-48 °C) [21] (yellow-brown); ir (KBr): ν 3406, 3303, 3161, 2977, 2926, 1632, 1597, 1445, 1364, 1260, 1163, 1105, 1052, 835, 798, 670, 638 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.19 (d, *J* = 9.2 Hz, 1H, H-5), 6.72 (d, *J* = 9.2 Hz, 1H, H-4), 6.22 (br s, 2H, NH_2), 3.09 (q, *J* = 7.3 Hz, 2H, SCH_2), 1.26 ppm (t, *J* = 7.3 Hz, 3H, CH_3); ^{13}C nmr (DMSO-d_6): δ 158.64 (C-3), 149.47 (C-6), 127.88 (C-4 or C-5), 114.98 (C-4 or C-5), 24.41 (SCH_2), 14.51 ppm (CH_3); ms (ESI): 127, 110, 100 (100%), 96, 95, 79, 68, 61, 49; hrms (ESI) for $C_6H_{10}N_3S$ $[M+H]^+$: calcd 156.0595, found 156.0580.

3-Amino-6-propylthiopyridazine (**7**).

This compound was prepared with a reaction time of 53 hours; yield: 89%; eluent for flash column chromatography: $CHCl_3$-EtOH (95:5); mp 76 °C (lit 77-78 °C) [21] (white); ir (KBr): ν 3406, 3320, 3199, 2961, 2929, 2869, 1635, 1597, 1533, 1452, 1237, 1156, 1102, 1054, 1024, 832, 675, 637, 460 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.19 (d, *J* = 9.3 Hz, 1H, H-5), 6.70 (d, *J* = 9.3 Hz, 1H, H-4), 6.20 (br s, 2H, NH_2), 3.06 (t, *J* = 7.3 Hz, 2H, SCH_2), 1.62 (h, *J* = 7.3 Hz, 2H, CH_2), 0.96 ppm (t, *J* = 7.3 Hz, 3H, CH_3); ^{13}C nmr (DMSO-d_6): δ 158.67 (C-3), 149.64 (C-6), 127.95 (C-4 or C-5), 115.01 (C-4 or C-5), 32.11 (SCH_2), 22.26 (CH_2), 13.10 ppm (CH_3); ms (ESI): 128, 127, 111, 110, 100, 96 (100%), 95, 79, 47; hrms (ESI) for $C_7H_{12}N_3S$ $[M+H]^+$: calcd 170.0752, found 170.0746.

Synthesis of 3-Amino-6-phenylthiopyridazine (**9**) *via* Thiophenolysis of 3-Amino-6-chloropyridazine (**1**).

A mixture of 3-amino-6-chloropyridazine (**1**) (0.630 g, 4.86 mmol), sodium thiophenolate (2.83 g, 21.4 mmol) and 20 ml dry dioxane was stirred and heated under reflux (temperature of oil bath = 112 °C) under a nitrogen atmosphere for 60 hours. After cooling the crude reaction mixture was poured into 100 ml H_2O/150 ml EtOAc. The organic layer was separated, dried over $MgSO_4$ and evaporated to dryness. The residue was purified by flash column chromatography on silica gel with EtOAc as eluent (the mixture was brought on column dissolved in CH_2Cl_2) yielding **9** (0.97 g, 98%) as a white solid; mp 132 °C (lit. 139-140 °C) [21] (white); ir (KBr): ν 3303, 3164, 1633, 1587, 1537, 1450, 1189, 1154, 1081, 1026, 834, 747, 638, 550, 510, 455 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.38-7.25 (m, 5H, Ph), 7.12 (d, *J* = 9.2 Hz, 1H, H-5), 6.73 (d, *J* = 9.2 Hz, 1H, H-4), 6.52 ppm (br s, 2H, NH_2); ^{13}C nmr (DMSO-d_6): δ 160.24 (C-3), 150.26 (C-6), 134.52 (C-1'), 131.57 (C-3',5'), 131.20 (C-4'), 130.17 (C-2',6'), 128.21 (C-4 or C-5), 116.00 ppm (C-4 or C-5); ms (ESI): 204 (100%), 109, 71; hrms (ESI) for $C_{10}H_{10}N_3S$ $[M+H]^+$: calcd 204.0595, found 204.0576.

Acknowledgements.

We thank J. Aerts, W. Bollaert, R. Philippeth, J. Schrooten, W. Van Dongen, V. Van Heurck, W. Van Lierde, N. Verhaert and J. Verreydt for technical assistance and Prof. Dr. E. Esmans for the use of his MS facilities. Bert U. W. Maes is grateful for a grant from the foundation 'Rosa Blanckaert'.

REFERENCES AND NOTES

[1] G. B. Barlin, *J. Heterocyclic Chem.*, **35**, 1205 (1998) and references cited therein.

[2] B. U. W. Maes, G. L. F. Lemière, R. Dommisse, K. Augustyns and A. Haemers, *Tetrahedron*, **56**, 1777 (2000).

[3] P. Fitton and E. A. Rick, *J. Organomet. Chem.*, **28**, 287 (1971).

[4] J. H. Clark, J. P. English, G. R. Jansen, H. W. Marson, M. M. Rogers and W. E. Taft, *J. Am. Chem. Soc.*, **80**, 980 (1958).

[5] E. Steck, R. Brundage and L. Fletcher, *J. Am. Chem. Soc.*, **76**, 3225 (1954).

[6] J. Druey, K. Meier and K. Eichenberger, *Helv. Chim. Acta*, **37**, 121 (1954).

[7] J. W. Mason and D. L. Aldous, in The Chemistry of Heterocyclic Compounds, Vol **28**, R. N. Castle, ed, John Wiley and

Sons Inc., New York, 1973, p 54.

[8] T. Horie, K. Kinjo and T. Ueda, *Chem. Pharm. Bull.*, **10**, 580 (1962).

[9] E. Abignente, F. Arena, P. De Caprariis and L. Parente, *IL Farmaco Ed. Sci.*, **32**, 430 (1977).

[10] E. Abignente, F. Arena, E. Luraschi, C. Saturnino, E. Marmo, L. Berrino and D. Donnoli, *IL Farmaco*, **45**, 1075 (1990).

[11] E. Abignente, F. Arena, E. Luraschi, C. Saturnino, F. Rossi, L. Berrino and M. L. Cenicola, *IL Farmaco*, **47**, 931 (1992).

[12] L. Luraschi, F. Arena, A. Sacchi, S. Laneri and E. Abignente, *IL Farmaco*, **50**, 349 (1995).

[13] G. B. Barlin, L. P. Davies, S. J. Ireland, M. M. L. Ngu and J. Zhang, *Aust. J. Chem.*, **45**, 731 (1992).

[14] G. B. Barlin, L. P. Davies, S. J. Ireland, M. M. L. Ngu and J. Zhang, *Aust. J. Chem.*, **45**, 877 (1992).

[15] G. B. Barlin, L. P. Davis and P. W. Harrison, *Aust. J. Chem.*, **48**, 1031 (1995).

[16] P. W. Harrison, G. B. Barlin, L. P. Davies, S. J. Ireland, P. Matyus and M. G. Wong, *Eur. J. Med. Chem.*, **31**, 651 (1996).

[17] P. Matyus, G. B. Barlin, P. W. Harrison, M. G. Wong and L. P. Davies, *Aust. J. Chem.*, **49**, 435 (1996).

[18] G. B. Barlin, L. P. Davis, P. W. Harrison, S. J. Ireland and A. C. Willis, *Aust. J. Chem.*, **49**, 451 (1996).

[19] G. B. Barlin, *J. Chem. Soc. Perkin Trans. 1*, **40**, 1424 (1976).

[20] G. B. Barlin, L. P. Davies, S. J. Ireland and M. M. L. Ngu, *Aust. J. Chem.*, **42**, 1133 (1989).

[21] G. B. Barlin and S. J. Ireland, *Aust. J. Chem.*, **40**, 1491 (1987).

[22] G. B. Barlin, L. P. Davies, B. Glenn, P. W. Harrison and S. J. Ireland, *Aust. J. Chem.*, **47**, 609 (1994).

[23] G. B. Barlin, L. P. Davies, P. W. Harrison, N. W. Jacobsen and A. C. Willis, *Aust. J. Chem.*, **47**, 1989 (1994).

[24] G. B. Barlin, L. P. Davies, R. A. Davis and P. W. Harrison, *Aust. J. Chem.*, **47**, 2001 (1994).

[25] D. J. Brown, in The Chemistry of Heterocyclic Compounds, Vol **57**, E. C. Taylor and P. Wipf , eds, John Wiley and Sons Inc., New York, 2000, p 223 - 224.