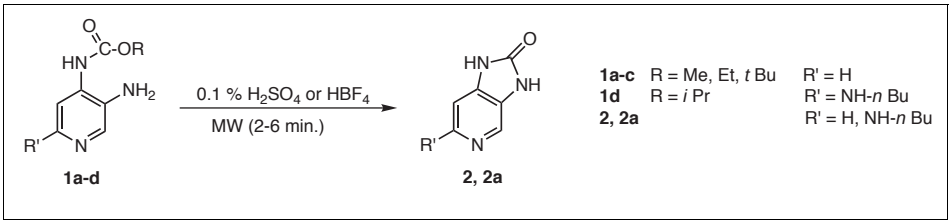
Jarle Holt, Jan M. Bakke and Anne Fiksdahl(*)

Department of Chemistry, Sem Sælands v. 8, Norwegian University of Science and Technology, NTNU, NO-7491 Trondheim, NORWAY.
e-mail: Anne.Fiksdahl@chem.ntnu.no

Received June 26, 2005




A facile acid catalysed cyclisation method for the preparation of the cyclic urea 2*H*-imidazo[4,5-*c*]pyridin-2-one (**2**) in > 95 % yield is reported. The biologically active compound **2** can be obtained by heating (3-amino-4-pyridinyl)-carbamic acid methyl, ethyl or *tert*-butyl esters (**1a-c**) in sulfuric acid (0.1 %) or in aqueous $HBF_4$ (3.5 equivalents) for 10 min. - 3 hrs at 90 °C. The corresponding microwave-promoted (MW) reactions afforded the pure product **2** within few minutes. The 6-butylamino-substituted analogue (**2a**) was correspondingly obtained by MW irradiation in 99 % yield by cyclisation of 2-(butylamino)-5-amino-4-pyridylcarbamic acid isopropyl ester (**1d**). Quantitative precipitation of product **2** was obtained by pH adjustment. The process represents a solvent-free, "green" method for the preparation of **2**.

*J. Heterocyclic Chem.*, **43**, 787 (2006).

## Introduction.

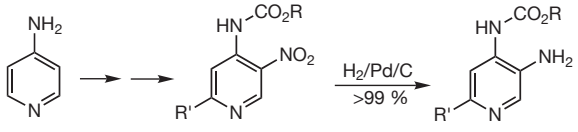
The cyclic urea compound, imidazo[4,5-*c*]pyridin-2-one (**2**, see Scheme 2), has been patented for its antiviral and antibacterial activity [1-3] and has previously been prepared by reaction of 3,4-diaminopyridine with CO and a stoichiometric or excess amount of Se in the presence of *N*-methylpyrrolidine [4]. Recently this biologically active cyclic urea was also prepared from 3-amino-4-pyridyl methyl and *tert*-butyl carbamates **1a** and **1c** [5]. However, the cyclisation reactions proved to be difficult and respectively 74 and 56 % yield were eventually obtained by heating at 150 °C in diglyme for 24 hours. The 6-butylamino-substituted analogue (**2a**) was made by the same procedure in 55 % yield from 2-(butylamino)-5-amino-4-pyridylcarbamic acid *tert*-butyl ester. Imidazolopyridines have correspondingly been prepared from 4-acetamido- and 4-benzamido-3-aminopyridine [6].

We hereby report a more convenient method for the quantitative preparation of imidazolopyridinones (**2,2a**) by less vigorous reaction conditions. The key substrates for our syntheses are 4-amino-3-nitropyridines, which have now been readily available through an improved nitration method [7,8]. Our results are discussed below.

## Results and Discussion.

The 3-amino-4-pyridyl carbamate substrates (**1a-d**) were prepared as shown in Scheme 1. The nitration of 4-aminopyridine was carried out after protection of the 4-amino group by alkoxycarbonyl to give **3a-d** [5,6]. Methyl and ethyl carbamates **3a** have also been prepared by nitration of methyl/ethyl 4-pyridylcarboxylate followed by hydrazide formation, diazotization and Curtius rearrangement of the acyl azide in methanol/ethanol [10]. The 3-aminopyridyl carbamates (**1a-d**) were obtained by selective reduction of the nitro group in quantitative yield by catalytic hydrogenation. 3,4-Diaminopyridine [11], which also may be a suitable substrate for the preparation of (**2**) [12], has readily been prepared based on the improved nitration method, affording higher yields [6] compared to previous methods [13].

Scheme 1




3-Amino-4-pyridyl carbamates (**1a-c**) afforded the imidazolopyridine product (**2**) by harsh conditions heating in 2 % sulfuric acid. However, we experienced that the direct cyclisation of the 3-amino-4-carbamates (**1a-c**) to give **2** was also successful at lower concentrations of

Table 1

Cyclisation of **1a-c** to **2**, reaction conditions.

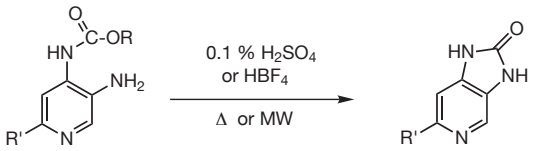
| Catalyst | Amount | Temp. | Reaction time | Conversion to 2 [a] | Yield [b] |
|---|---|---|---|---|---|
| $H_2SO_4$ | 0.1 % | 90 °C | 10-30 min., 5 mg[c] | 99% | |
| | | | 3 hrs., 100 mg[d] | 99 % | > 95 % |
| | 0.1 % | 40 °C | 8 hrs., 5 mg[c] | 40 % | |
| $HBF_4$ | 3.5 eqv. | 90 °C | 10-30 min., 5 mg[c] | 99 % | |
| | | | 1-3 hrs, 100 mg[d] | 99 % | > 95 % |
| | 0.65 eqv. | 90 °C | 5 hrs., 5 mg[c] | 99 % | |
| | 7 eqv. | 40 °C | 8 hrs., 5 mg[c] | 0 % | |

[a] Conversion is based on 1H nmr of crude product, [b] Yield after work-up, [c] All substrates, 1a-c, [d] Substrate 1a,c

sulfuric acid (see Scheme 2 and Table 1). Full conversion of the carbamates (**1a-c**, 5-100 mg) to the cyclic urea (**2**) was obtained after 10 min.-3 hours by heating at 90 °C even with 0.1 % sulfuric acid. The catalytic cyclisation of *tert*-butyl carbamate (**1c**) was faster than the methyl and ethyl carbamates (**1a,b**). Prolonged reaction time (3 hrs.) was required for larger batches (100 mg). Longer reaction time (5 mg, 8 hrs.) was also needed when the reaction was carried out at lower temperature (40 °C). The methyl, ethyl and *tert*-butyl carbamates (**1a-c**) did also readily undergo complete cyclisation (5 mg, 30 min.) when sulfuric acid was replaced with 3.5 equivalents of aqueous $HBF_4$. Longer reaction time (5 mg, 5 hrs.) was needed when the number of equivalents of $HBF_4$ was reduced (0.65 equivalent). However, no cyclisation took place at lower temperature (40 °C), even with longer reaction time (8 hrs.) and increased number of equivalents of $HBF_4$ (7 equivalents).

A one-pot procedure including the previous reduction (Pd/C, $H_2$) and the final cyclisation steps to give **2** in 95 % yield directly from **3a-c** was also successful. This would be the method of choice for the preparation of **2**.

Scheme 2




**1a-d** **2, 2a**

**1a** R = Me, R' = H
**1b** R = Et R' = H
**1c** R = *t* Bu R' = H
**1d** R = *i* Pr R' = NH-*n* Bu

**2** R' = H
**2a** R' = NH-*n* Bu

Recent development in microwave-accelerated (MW) organic syntheses has shown that the method offers the great advantage of enhanced reaction rates. The products are often produced in higher yields and purity by such reactions compared to conventional methods.

We have experienced that MW promoted reactions have been successful for a number of reactions [9]. As shown in Table 2, complete conversion of the carbamates (**1a-c**, 5-100 mg) into the cyclic urea product **2** was obtained within 2-6 minutes of MW irradiation. The *tert*-butyl carbamate (**1c**) was the more reactive, as demonstrated by

Table 2

Cyclisation of **1a-d** to **2,2a** by microwave (MW) irradiation.s

| Substrate | Catalyst | MW irradiation, reaction time | Product, conversion [a] |
|---|---|---|---|
| **1a**, R = Me | 0.1 % $H_2SO_4$ | 4 min., 5 mg | **2**, 99 % |
| **1b**, R = Et | | 4 min., 5 mg | **2**, 99 % |
| **1c**, R = *t*-Bu | | 2 min., 5 mg | **2**, 99 % |
| **1d**, R = *i*Pr, R' = NH*n*Bu | | 2 min., 5 mg | **2a**, 99 % |
| **1b**, R = Me | 3.5 eqv. $HBF_4$ | 6 min., 5 mg | **2**, 99 % |
| **1c**, R = Et | | 6 min., 5 mg | **2**, 99 % |
| **1c**, R = *t*-Bu | | 2 min., 5 mg | **2**, 99 % |
| | | 2 min., 100 mg | **2**, 99 % [b] |
| **1c**, R = *t*-Bu | 0.65 eqv. $HBF_4$ | 2 min., 5 mg | **2**, 99 % |
| | | 3 min.,100 mg | **2**, 99 % [b] |
| | 0.2 eqv. $HBF_4$ | 8 min., 5 mg | **2**, 40 % |
| **1d**, R = *i*Pr, R' = NH*n*Bu | 3.5 eqv. $HBF_4$ | 6 min., 5 mg | **2a**, 99 % |

[a] Conversion is based on $^1$H nmr of crude product, [b] > 95 % yield after work-up

the lower reaction time compared to the methyl and ethyl substrates (**1a,b**). This is in correspondence to our observations by conventional heating. The reactions of **1a,b** in sulfuric acid were more rapid than in aqueous $HBF_4$. In contrast to our observations of cyclisation by conventional heating, the required reaction time for full MW conversion of larger batches (100 mg) was approximately the same as for small batches (5 mg).

The 6-alkylamino-substituted substrate **1d** was also included in the MW experiments. Similarly, full conversion to the corresponding cyclic urea **2a** was obtained within 2-6 min. of MW irradiation. Due to the low solubility of the butylamino substrate **1d** in water, these experiments were carried out in DMSO.

We experienced that the pH of the aqueous solution during the extraction work-up was particularly crucial for the yield of the urea product. Due to the urea moiety, only moderate yields were obtained by extraction at pH 9 - 12. The product could however, be quantitatively extracted by ethyl acetate from a neutral solution of pH 7. The recrystallised product was in general obtained in > 95 % yield. However, by adjustment of pH to 7, a spontaneous and quantitative precipitation of product **2** (pure by m.p. and $^1$H nmr) was observed when **2** was prepared from **1a**. This represents an even simpler work-up method for product **2** and completes the facile protocol for a solvent-free, "green" method for the preparation of **2**.

## Conclusion.

The biologically active cyclic urea, pyridoimidazolone (**2**) was prepared in > 95 % yield by acid catalysed cyclisation from (3-amino-4-pyridinyl)-carbamic acid methyl, ethyl or *tert*-butyl ester (**1a-c**) by heating (90 °C / 10 min.-3 hrs) in sulfuric acid (0.1 %) or in aqueous $HBF_4$ (3.5 equivalents). Correspondingly, the microwave-promoted (MW) reactions afforded the pure product **2** quantitatively within few minutes. The 6-butylamino-substituted analogue (**2a**) was also prepared by MW irradiation (99 %) by cyclisation of the precursor **1d**. Quantitative precipitation of product **2** was obtained by pH adjustment of the reaction mixture. Our conditions were thus excellent for the simple preparation of the five-membered cyclic urea product (**2**), which was obtained by less vigorous reaction conditions and in higher yield than previous methods. The facile protocol represents a solvent-free, "green" method for the preparation of **2**.

## EXPERIMENTAL

Solvents: pro analysi quality. $^1$H / $^{13}$C nmr: Bruker Avance DPX 300 and 400 MHz spectrometers, chemical shifts are reported in ppm downfield from TMS. J values are given in Hz. ms: Finnigan MAT 95 XL (EI / 70 eV). ir: Nicolet 20SXC FT-IR spectrophotometer. All melting points are uncorrected, measured by Griffin apparatus. Flash chromatography: Silica (sds, 60 A, 40-63 μm). Microwave irradiation was performed in a microwave oven (Elram M8017NP-CF) at "Low" power (17 % of max 800 W output). Methyl and *tert*-butyl carbamates (**1a,c**) were prepared according to the literature [5].

3-Nitro-4-pyridylcarbamic acid ethyl ester (**3b**).

**3b** was prepared from 4-aminopyridine by nitration of the corresponding carbamate according to the literature for the preparation of **3a,c** [5]. All data (mp, ir, $^1$H and $^{13}$C nmr, ms) were in accordance with our previous data for **3b** prepared *via* Curtius rearrangement [10].

3-Amino-4-pyridinylcarbamic acid ethyl ester (**1b**).

The compound was prepared by reduction of **3b** according to the literature for the preparation of **1a,c** [5]. **3a** (500 mg, 2.37 mmol) was dissolved in methanol (10 ml) and added Pd/C (5 %, 83 mg). The solution was stirred for 16 hrs. under $H_2$ pressure (10 bar). The solution was filtered and off-white crystals (430 mg, 99 %), pure by $^1$H and $^{13}$C nmr, was obtained; mp 125 - 127 °C; ir (KBr) 3388m, 3212w, 2982w, 1727s, 1589s, 1516s, 1480m, 1252s, 1211m, 1068s, 870m, 832m, 767m cm$^{-1}$; $^1$H nmr (300 MHz, $CDCl_3$): $\delta$ 1.33, (t, J 7.1, 3H), 3.44 (br, 2H), 4.25 (q, J 7.1, 2H), 7.09 (br., 1H), 7.64 (d, J 5.4, 1H, H-5), 8.10 (d, J 5.4, 1H, H-6), 8.14 (s, 1H, H-2); $^{13}$C nmr (75 MHz, $CDCl_3$): $\delta$ 14.6, 62.1, 114.6, 132.3, 134.8, 140.6, 142.9, 153.7; ms: m/z 181 ($M^+$, 100 %), 153 (2), 135 (38), 122 (9), 108 (33), 93 (4), 81 (16);

*Anal*. Calcd. for $C_8H_{11}N_3O_2$: C, 53,03; H, 6,12; N, 23,19. Found: C, 52.71; H, 6.12; N, 24.61.

2-Butylamino-5-amino-4-pyridylcarbamic acid isopropyl ester (**1d**).

This intermediate was prepared by hydrogenation of 2-*N*-butylamin-5-nitro-4-pyridylcarbamic acid isopropyl ester according to literature [5]. The solution was filtered and a purple solid (98 %), pure by $^1$H nmr, was obtained. The product decomposed by flash chromatography and was therefore used in the next step without further purification. ir (neat) 3411w, 3004m, 2925w, 1716s, 1420m, 1363s, 1222s, 1092m, 902w cm$^{-1}$; $^1$H nmr (300 MHz, $CDCl_3$): $\delta$ 0.96, (t, J 5.4, 3H, $CH_3$), 1.31 (d, J 4.5, 6H, 2 $CH_3$), 1.41 (dt, J 5.4, 2H, $CH_2$), 1.58 (m, 2H, $CH_2$), 2.71 (br, $NH_2$), 3.21 (br, s, 2H, NH-$CH_2$), 4.34 (br, s, NH), 5.02 (hept, J 4.5, CH), 7.14 (s, 1H, H-3), 7.63 (br, NH), 7.70 (s, 1H, H-6); $^{13}$C nmr (100 MHz, $CDCl_3$): $\delta$ 13.8, 20.1, 21.0, 31.6, 42.4, 69.0, 94.1, 119.6, 141.5, 141.7, 152.8, 156.9; ms: m/z 266 ($M^+$, 37 %), 224 (12), 205 (27), 191 (43), 177 (57), 163 (34), 151 (52), 137 (88), 84 (57), 66 (100).

1,3-Dihydro-2*H*-imidazo[4,5-*c*]pyridin-2-one (**2**).

General procedure using i) sulfuric acid or ii) $HBF_4$.

The alkyl carbamate (**1a-c**, approx. 5 mg, 0.025 mmol, 1 eqv.) was dissolved in i) 0.1 % sulfuric acid (0.5 ml) or ii) a solution of water (0.5 ml) and aqueous $HBF_4$ (50 %, 0.09 mmol, 3.5 eqv.) and heated. By both methods $^1$H nmr of the crude product showed complete conversion of the carbamates (**1a-c)** to the cyclic urea product **2** after heating of the solution (90 °C) for 10 min.(**1c**)/30 min. (**1a,b**). See Table 1 for other reaction conditions. Three hours reaction time was needed for 100 mg batches in 5 ml solution. Alternatively, corresponding batches of **1a-c** (5-100 mg in 0.5-5 ml solutions) were irradiated in a

microwave oven for 2-6 min. to give full conversion to product **2**, see Table 2. From all reactions product **2** could be quantitatively extracted by ethyl acetate after pH adjustment of the solution to 7 by the addition of a NaOH solution (10 %). When prepared from the methyl carbamate (**1a**, 100 mg), spontaneous quantitative precipitation of product **2**, (pure by m.p., $^{1}$H and $^{13}$C nmr), was obtained directly by pH adjustment. The recrystallised product **2** was obtained in > 95 % yield. Alternatively, **2** could be prepared directly in 95 % isolated yield directly from **3a-c** in a one-pot procedure by reduction (Pd/C-$H_2$) *via* **1a-c** and cyclisation by heating or MW. This would be the method of choice for the preparation of **2**. All data (mp, ir, $^{1}$H and $^{13}$C nmr, ms) were in accordance with literature [5].

6-(Butylamino)-1,3-dihydro-*2H*-imidazo[4,5-*c*]pyridin-2-one (**2a**).

The product was prepared in 99 % yield by MW irradiation from **1d** as described for the preparation of **2**, i) or ii) above, see Table 2. Water was however replaced by DMSO. Spectroscopic data were in accordance with literature [5].

Acknowledgements.

Financial support from the Research Council of Norway is gratefully acknowledged.

REFERENCES

[1] R. B. Borgens, R. Shi, S. R. Byrn, D. T. Smith, *WO 2004052291* (2004); *Chem. Abstr.*, **141**, 47362 (2004).

[2] G. V. DeLucca, *US 5763469* (1998); *Chem. Abstr.*, **129**, 67775 (1998).

[3] G. V. DeLucca Q. Han, P. K. Jadhav, J. M. Kassir, P. Y.-S. Lam, R. J. Mchugh, Jr., *WO 9708150* (1997); *Chem. Abstr.*, **126**, 264100 (1997).

[4] T. Yoshida, N. Kambe, S. Murai, N. Sonoda, *Bull. Chem. Soc. Japan* **60**, 1793 (1987).

[5] J. M Bakke, H. S. H. Gautun, H. Svensen, *J. Heterocyclic Chem.*, **40**, 585 (2003).

[6] J. M. Bakke, J. Riha, *J. Heterocyclic Chem.*, **30**, 1143 (1999).

[7] J. M. Bakke, I. Hegbom, K. Øvreeide, K. Aaby, *Acta Chem. Scand.*, **48**, 1001 (1994).

[8] J. M. Bakke, E. Ranes, *Synthesis,* 281 (1997).

[9] F. Tjosås, A. Fiksdahl, *J. Heterocyclic Chem.*, (2005) *in prep.*

[10] J. Holt, T. Andreassen, J. M. Bakke and A. Fiksdahl, *J. Heterocyclic Chem.*, **42**, 259 (2005).

[11] O. Bremer, *Justus Liebigs Ann. Chem.* **518**, 274 (1935).

[12] I. Torrini, G. P. Zeccini, F. Agrosi, and M. P. Paradisi, *J. Heterocyclic Chem.*, **22**, 313 (1985).

[13] J. B. Campbell, J. M. Greene, E. R. Lavagnino, D. N. Gardner, A. J. Pike, J. Snoddy, E. C. Taylor, *J. Heterocyclic Chem.*, **23**, 669 (1986).