Synthesis of Novel N-Pyridylcantharidinimides by Using High Pressure

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The recently described pressure reaction in the presence of trithylamine with subsequent thermal (200°C) cyclization provided 13N-pyridylcantharidinimides **4a-4m** from aminopyridines and cantharidin in yields of 15-83%. 2-Amino-3,5-dichloropyridine failed to yield **4n**.

INTRODUCTION

Some of us described recently an improved synthesis of cantharidinimides.[1] The usual heating to 200 °C of cantharidin **1** with the primary amines[2,3,4] was performed with the solvent toluene in a sealed tube preventing an evaporation of cantharidin as well as of the amine, if this is volatile. Addition of triethylamine (TEA) countered the protonation of the primary amine by the monoamide monocarboxylic acid **2** that arises in the first step of the synthesis (Scheme I). Potential bioactivity[2,3,4,5] stimulated research on cantharidinimides and related imides. The present investigation extended the improved synthesis in order to obtain a novel type of cantharidinimides in usable yields and to simultaneously study the scope of this synthesis. The first mechanistic step, the attack of the primary amine on a carbonyl carbon of **1**, is very difficult for steric reasons. It requires heat and depends necessarily on the nucleophilicity of the primary amine.

RESULTS AND DISCUSSION

Neglecting steric shielding of the NH_2 group, this nucleophilicity should closely be related to the thermodynamic basicity. One may therefore expect that formation of **2** (Scheme I) and hence also that one of the respective cantharidinimide will become more difficult when the amine basicity decreases, e.g., in aromatic amines. N-Phenylcantharidinimide has previously been prepared from **1** and aniline but this report did not mention the yield.[2] We obtained now 63% of this compound using pressure synthesis. This encouraged us to extend the pressure synthesis to reactions of **1** with aminopyridines that should provide hitherto unknown N-pyridylcantharidinimides. The NH_2 basicity of aminopyridines is unknown but will be slightly less than that one of the corresponding anilines due to the electron deficiency of the pyridine ring. Of course, the *ring nitrogen* basicity may be rather high in α- and γ-aminopyridines where both nitrogen

Scheme I

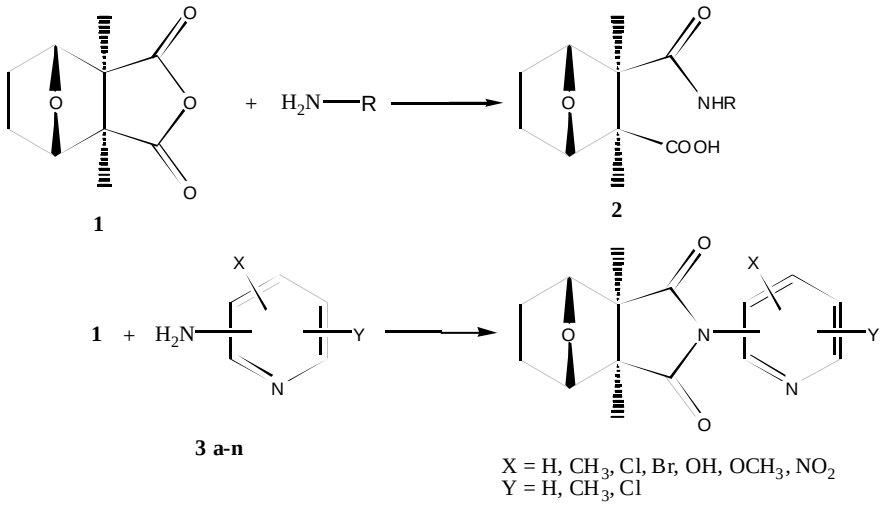
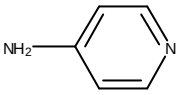
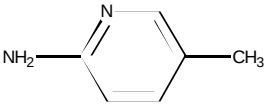
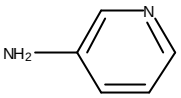
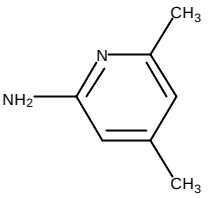
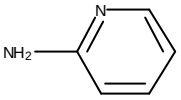
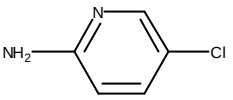
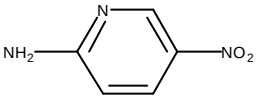
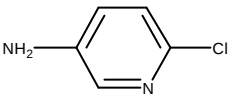
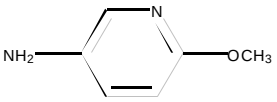
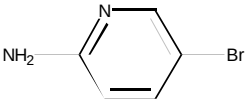
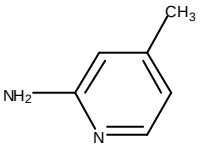
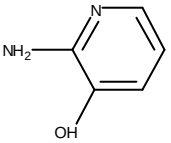
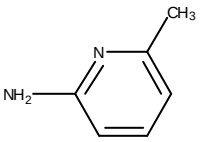
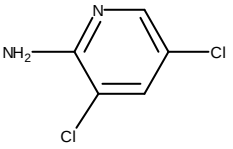
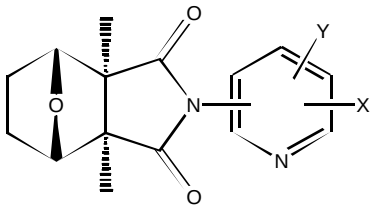


Table 1. Preparation of N-Pyridylcantharidinimides **4a-4n**

Entry	Amine	Product	Yield (%)[a]	Entry	Amine	Product	Yield (%)[a]
1	**3a** 	**4a**	62	8	**3h** 	**4h**	37
2	**3b** 	**4b**	29	9	**3i** 	**4i**	72
3	**3c** 	**4c**	39	10	**3j** 	**4j**	50
4	**3d** 	**4d**	15	11	**3k** 	**4k**	28
5	**3e** 	**4e**	83	12	**3l** 	**4l**	35
6	**3f** 	**4f**	57	13	**3m** 	**4m**	79
7	**3g** 	**4g**	47	14	**3n** 	**4n**	0

[a] Yields obtained after purification by Chromatograph on silica gel.



X = H, CH_3, Cl, Br, OH, OCH_3, NO_2
Y = H, CH_3, Cl

atoms are part of an amidine structure or of an vinylogous amidine.

As shown by Table 1, the N-pyridylcantharidinimides **4a-4m** could be prepared by means of pressure synthesis. The yield (after crystallization from methanol) vary from 15% to 83% and show a trend compatible with the expected basicity influence of **3**. The highest yields were obtained from methoxypyridine **3e** and hydroxypyridine **3m**. The pKa values [6] of the two anilines, or ratyer anilinium ions, corresponding to **3e** and **3m** are 5.3-5.4 and ca. 4.8, i.e. slightly higher than ca. 4.6 for the parent anline whose pyridine counterparts are **3a-3c**. The variation in yields of **4a-4c** may perhaps reflect the inductive electron withdrawal by the ring nitrogen, since an inductive effect will inversely increase with the distance between the two nitrogen atoms. However, one should not overstress this whole topic since the yield obtained by preparative techniques will also be influenced by other factors that can cause a strong variation. The results obtained with **3d** and **3n**, however, strongly confirm the influence of amine nucleophilicity and basicity. Pka of the anline counterpart is ca. 1.0 for **3d** and 2.0-2.6 for **3n**. The failure to obtain **4n** can be explained by the combined influence of low basicity and steric hindrance. The latter must be extremely effective in the reaction with the sterically shielded carbonyl of **1**.

EXPERIMENTAL SECTION

General Methods

Melting points were determined with a melting point microscope (Yanaco apparatus) and Büchi melting point B-545. Silica gel (0.063-0.200 mm, 70-230 mm mesh if not otherwise stated, else 0.040-0.063 mm, 230-400 mesh) supplied by Merck was used for column chromatography. Infrared spectra were recorded on a Perkin Elmer Model 882 and a Nicolet 510 PFT-IR spectrophotometer. Mass spectra were obtained on a Joel JMSHX 110 FABMS and Joel JMS-HX 110 for high resolution spectrometers. ^{1}H NMR spectra ($CDCl_3$ unless otherwise stated) were recorded at 200 MHz and at 300 MHz on Bruker AC spectrometers. Chemical shifts are shown in δ values (ppm) with tetramethylsilane (TMS) as an internal reference.

General Procedure

General Procedure for the Reaction of Cantharidinimides. The synthesis both followed the general method and used the sealed tube described in Ref. 1. Amine (1 mmol of **3** or aniline), **1** (1 mmol), TEA (2 mL) and toluene (3 mL) were heated to 200 °C for 2 h under stirring in the sealed tube. After cooling to room temperature, toluene and TEA were evaporated. The residue was heated to 200 °C for another 1 h and was subsequently subjected to column chromatography (silical gel, $CHCl_3$: MeOH = 9 : 1). The product was recrystallized from methanol.

N-Phenylcantharidinimide

Cantharidin (197 mg, 1.0 mmole), amine (110 mg, 1.2 mmole), TEA (3 mL), Toluene (3 mL), 62% yield; m.p. 123-124 °C (MeOH) (lit.[2] 120-122 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.24 (s, 6H), 1.72-1.86 (m, 4H), 4.69 (t, 2H, J = 2.6 Hz), 7.26 (d, 2H, J = 8.0 Hz, Phenyl H-3, H-5), 7.45 (dd, 2H, J = 7.2 Hz, 8.4 Hz, phenyl H-2, H-6); IR (KBr), 1710, 1766 (imide) cm^{-1}; MS *m/z* (rel. int. %), 272 (M^+, 10), 202 (70), 96 (100).

N-(4-Pyridyl)cantharidinimide (4a)

Cantharidin (197 mg, 1.0 mmole), amine (105 mg, 1.1 mmole), TEA (1 mL), Toluene (3 mL), 61% yield; m.p. 135-136 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz), δ 1.26 (s, 6H), 1.73-1.91 (m, 4H), 4.69 (t, 2H, J = 2.6 Hz), 7.43 (dd-like, 2H, J = 1.2, 6.0 Hz, pyridyl H-2, H-6), 8.71 (d, 2H, J = 4.1, pyridyl H-3, H-5); IR (KBr), 1717, 1772 (imide) cm^{-1}; MS *m/z* (rel. int. %), 272 (M^+, 20), 204 (100), 96 (45); HRMS (EI) calcd. for $C_{15}H_{16}O_3N_2$ 272.1161, found: 272.1158.

N-(3-Pyridyl)cantharidinimide (4b)

Cantharidin (197 mg, 1.0 mmole), amine (129 mg, 1.4 mmole), TEA (2 mL), Toluene (3 mL), 29% yield; m.p. 108-109 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz), δ 1.27 (s, 6H), 1.73-1.91 (m, 4H), 4.69 (t, 2H, J = 2.6 Hz), 7.43 (dd, 2H, J = 4.8, 8.1 Hz, pyridyl H-4), 7.73 (dt, 1H, J = 1.7, 4.5, 8.1 Hz, pyridyl H-5), 8.62 (dd, 1H, J = 7.6, 5.3 Hz, pyridyl H-6), 8.63 (d, 1H, J = 1.8 Hz, pyridyl H-2); IR (KBr), 1713, 1767 (imide) cm^{-1}; MS *m/z* (rel. int. %) 272 (M^+, 20), 204 (100), 96 (47); HRMS (EI) calcd. for $C_{15}H_{16}O_3N_2$ 272.1161, found: 272.1154.

N-(2-Pyridyl)cantharidinimide (4c)

Cantharidin (196 mg, 1.0 mmole), amine (95 mg, 1.0 mmole), TEA (2 mL), Toluene (5 mL), 39% yield; m.p. 154-155 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz), δ 1.27 (s, 6H), 1.73-1.90 (m, 4H), 4.72 (t, 2H, J = 2.6 Hz), 7.35 (dd, 2H, J = 2.4, 8.0 Hz, pyridyl H-3, H-5), 7.87 (dt, 1H, J = 1.9, 5.0, 7.9 Hz, pyridyl H-4), 8.65 (d, 1H, J = 5.4 Hz, pyridyl H-6); IR (KBr) 1711, 1772 (imide) cm^{-1}; MS *m/z* (rel. int. %), 272 (M^+, 20), 96 (30), 203 (100); HRMS (EI) calcd. for $C_{15}H_{16}O_3N_2$

272.1161, found: 272.1184.

N-(5-Nitropyridyl-2)cantharidinimide (4d)

Cantharidin (196 mg, 1.0 mmole), amine (139 mg, 1.0 mmole), TEA (3 mL),Toluene (3 mL), 15% yield; m.p. 193-194 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz), δ 1.29 (s, 6H), 1.76-1.90 (m, 4H), 4.75 (t, 2H, *J* = 2.4 Hz), 7.63 (d, 1H, *J* = 8.7 Hz, pyridyl H-3), 8.63 (d, 1H, *J* = 8.8 Hz, pyridyl H-4), 9.45 (d, 1H, *J* = 2.6 Hz, pyridyl H-6); IR (KBr) 1714, 1780 (imide) cm^{-1}; MS (rel. int. %), 318 (M^+, 20), 274 (60), 248 (100); HRMS (EI) calcd. for $C_{15}H_{15}O_5N_3$ 317.1012, found; 317.1002.

N-(6-Methoxypyridyl-3)cantharidinimide (4e)

Cantharidin (200 mg, 1.02 mmole), amine (126 mg, 1.02 mmole) TEA (2 mL), To lu ene (5 mL), 83% yield; m.p. 154-155 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz), δ 1.25 (s, 6H), 1.73-1.88 (m, 4H), 3.95 (s, 3H), 4.69 (t, 2H, *J* = 2.6 Hz), 6.81 (d, 1H, *J* = 8.8 Hz, pyridyl H-4), 7.52 (dd, 1H, *J* = 2.7, 8.8 Hz, pyridyl H-5), 8.13 (d, 1H, *J* = 2.6 Hz, pyridyl H-2); IR (KBr) 1710, 1764 (imide) cm^{-1}; MS *m/z* (rel. int. %), 302 (M^+, 100), 233 (95), 96 (90); HRMS (EI) calcd. for $C_{16}H_{18}O_4N_2$ 302.1267, found: 302.1275.

N-(4-Methylpyridyl-2)cantharidinimide (4f)

Cantharidin (197 mg, 1.0 mmole), amine (110 mg, 1.0 mmole), TEA (2 mL), Toluene (6 mL), 57% yield; m.p. 157-158 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz), δ 1.27 (s, 6H), 1.74-1.87 (m, 4H), 2.42 (s, 3H, pyridyl 3-CH_3), 4.73 (t, 2H, *J* = 2.4 Hz), 7.16 (s, 1H, pyridyl H-3), 7.18 (d, 1H, *J* = 5.2 Hz, pyridyl H-5), 8.50 (d, 1H, *J* = 5.0 Hz, pyridyl H-6); IR (KBr) 1713, 1772 (imide) cm^{-1}; MS *m/z* (rel. int. %), 286 (M^+, 10), 217 (100), 96 (20); HRMS (EI) calcd. for $C_{16}H_{18}O_3N_2$ 286.1317, found: 286.1318.

N-(6-Methylpyridyl-2)cantharidinimide (4g)

Cantharidin (206 mg, 1.06 mmole), amine (137 mg, 1.27 mmole), TEA (2 mL), To lu ene (5 mL), 47% yield; m.p. 196-197 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.27 (s, 6H), 1.74-1.90 (m, 4H), 2.59 (s, 3H, pyridyl 6-CH_3), 4.72 (t, 2H, *J* = 2.2 Hz), 7.09 (d, 1H, *J* = 7.8 Hz, pyridyl H-3), 7.21 (d, 1H, *J* = 7.6 Hz, pyridyl H-5), 7.72 (dd-like, 1H, *J* = 7.7, 7.8 Hz, pyridyl H-4); IR (KBr) 1711, 1774 (imide) cm^{-1}; MS *m/z* (rel. int. %) 286 (M^+, 8), 217 (100), 96 (18); HRMS (EI), calcd. for $C_{16}H_{18}O_3N_2$ 286.1317, found: 286.1318.

N-(5-Methylpyridyl-2)cantharidinimide (4h)

Cantharidin (196 mg, 1.0 mmole), amine (108 mg, 1.0 mmole), TEA (3 mL), Toluene (5 mL), 37% yield; m.p. 189-190 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.26 (s, 6H), 1.73-1.89 (m, 4H), 2.38 (s, 3H, pyridyl 5-CH_3), 4.72 (d, 2H, *J* = 2.2 Hz), 7.22 (d, 1H, *J* = 8.1 Hz, pyridyl H-4), 7.65 (d, 1H, *J* = 8.1 Hz, pyridyl H-3), 8.46 (s, 1H, pyridyl H-6); IR (KBr) 1711, 1775 (imide) cm^{-1}; MS *m/z*, (rel. int. %), 286 (M^+, 7), 217 (100), 96 (25); HRMS (EI), calcd. for $C_{16}H_{18}O_3N_2$ 286.1317, found: 286.1366.

N-(4,6-Dimethylpyridyl-2)cantharidinimide (4i)

Cantharidin (205 mg, 1.05 mmole), amine (128 mg, 1.05 mmole), TEA (2 mL), To lu ene (10 mL), 72% yield; m.p. 181-183 °C (MeOH); ^{1}H NMR ($CDCl_3$, 200 MHz), δ 1.25 (s, 6H), 1.70-1.89 (m, 4H), 2.33 (s, 3H, pyridyl 4-CH_3), 2.52 (s, 3H, pyridyl 6-CH_3), 4.70 (t, 2H, *J* = 2.5 Hz), 6.89 (s, 1H, pyridyl H-5), 7.02 (s, 1H, pyridyl H-3); IR (KBr) 1710, 1778 (imide) cm^{-1}; MS *m/z* (rel. int. %) 300 (M^+, 8), 217 (100), 96 (18); HRMS (EI) calcd. for $C_{17}H_{20}O_3N_2$ 300.1473, found: 300.1480.

N-(5-Chloropyridyl-2)cantharidinimide (4j)

Cantharidin (196 mg, 1.0 mmole), amine (129 mg, 1.0 mmole), TEA (3 mL), Toluene (2 mL), 50% yield; m.p. 148-151 °C (MeOH); ^{1}H NMR ($CDCl_3$, 200 MHz), δ 1.27 (s, 6H), 1.74-1.89 (m, 4H), 4.71 (dd, 2H, *J* = 2.2, 4.5 Hz), 7.32 (d, 1H, *J* = 8.6 Hz, pyridyl H-3), 7.82 (dd, 1H, *J* = 2.9, 8.8 Hz, pyridyl H-4), 8.59 (d, 1H, *J* = 2.6 Hz, pyridyl H-6); IR (KBr) 1171, 1778 (imide) cm^{-1}; MS *m/z* (rel. int. %) 306 (M^+, 20), 237 (100) 96 (90); HRMS (EI) calcd. for $C_{15}H_{15}O_3N_2Cl$ 306.0771, found: 306.0793.

N-(6-Chloropyridyl-3)cantharidinimide (4k)

Cantharidin (150 mg, 0.8 mmole), amine (100 mg, 0.8 mmole), TEA (4 mL), Toluene (5 mL), 28% yield; m.p. 110-112 °C (MeOH); ^{1}H NMR ($CDCl_3$, 200 MHz), δ 1.27 (s, 6H), 1.79-1.90 (m, 4H), 4.70 (t, 2H, *J* = 2.6 Hz), 7.43 (d, 1H, *J* = 8.9 Hz, pyridyl H-3), 7.70 (dd, 1H, *J* = 2.8, 8.7 Hz, pyridyl H-4), 8.44 (d, 1H, *J* = 3.1 Hz, pyridyl H-2); IR (KBr) 1707, 1770 (imide) cm^{-1}; MS *m/z* (rel. int. %) 306 (M^+, 35), 237 (100), 96 (94); HRMS (EI), calcd. for $C_{15}H_{15}O_3N_2Cl$ 306.0771, found: 306.0768.

N-(5-Bromopyridyl-2)cantharidinimide (4l)

Cantharidin (113 mg, 0.6 mmole), amine (100 mg, 0.6 mmole), TEA (3 mL), Toluene (3 mL), 35% yield; m.p. 188-190 °C (MeOH); ^{1}H NMR ($CDCl_3$, 200 MHz), δ 1.28 (s, 6H), 1.74-1.90 (m, 4H), 4.69 (s, 2H), 7.28 (dd, 1H, *J* = 2.4, 7.4 Hz, pyridyl H-3), 8.00 (dd, 1H, *J* = 2.3, 10.2 Hz, pyridyl H-4), 8.70 (s, 1H. pyridyl H-6); IR (KBr) 1710, 1776 (imide) cm^{-1}; MS *m/z* (rel. int. %) 351 (M^+, 4) 352 (20), 353 (4), 281

(100), 282 (98); HRMS (EI) calcd. for $C_{15}H_{15}O_3N_2Br$ 351.0266, found: 351.0244.

N-(3-Hydroxypyridyl-2)cantharidinimide (4m)

Cantharidin (205 mg, 1.04 mmole), amine (120 mg, 1.09 mmole), TEA (2 mL), To lu ene (2 mL), 79% yield; m.p. over 300 °C (MeOH); ^{1}H NMR ($CDCl_3$, 200 MHz), δ 1.27 (s, 6H), 1.71-1.96 (m, 4H), 2.70 (sb, OH), 4.96 (dd, 2H, J = 2.1, 2.8 Hz), 7.27 (dd, 1H, J = 4.7, 8.2 Hz, pyridyl H-5), 7.41 (dd, 1H, J = 1.5, 8.2 Hz, pyridyl H-4), 8.13 (dd, 1H, J = 1.5, 4.5 Hz, pyridyl H-6); IR (KBr) 1713, 1776 (imide) cm^{-1}, 3737 (OH) cm^{-1}; MS *m/z* (rel. int. %), 288 (M^+, 30), 219 (100), 39 (60), 53 (45); HRMS (EI) calcd. for $C_{15}H_{16}O_4N_2$ 288.1110, found: 288.1169.

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Key Words

Cantharidinimide; Cantharidin; Aminopyridine.

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