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Oxidative halogenation of N-methylcytisine by halogenides and hydrogen peroxide in acidic medium

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ABSTRACT

New approach to halogen introduction into 2-pyridone core of quinolizidine alkaloid N-methylcytisine by oxidative halogenation with halogenides and hydrogen peroxide in acidic medium is developed.

KEYWORDS

Quinolizidine alkaloids;
(-)-cytisine;
Nicotine acetylcholine receptor;
Oxidative halogenation.

INTRODUCTION

Quinolizidine alkaloid (-)-cytisine is available from *Thermopsis, Cytisus, Genista, Maackia* and *Sophora* (Fabaceae) plants, and it is a well-known ligand of $\alpha_4\beta_2$ subtype of nicotine acetylcholine receptor (nACR)[1,2]. Within last twenty years this molecula became a popular template in drugs design for treatment of neurodegenerative diseases[3-12].

It is established that introduction of halogen into 2-pyridone core of (-)-cytisine (positions 3 or 5) significantly increases affinity to nACR[6-10]. In addition, the general strategy of synthesis of aryl, alkyl, alkenyl and alkinyl (-)-cytisine derivatives by cross-coupling reaction is based on analogous halogenation procedure at the first step[7,11,12]. Therefore elaboration of new convenient and effective approaches to (-)-cytisine halogenation is till now the important problem.

While halogenation of the 2-pyridone core of (-)-cytisine by action of molecular halogens and N-halosuccinimides has been studied in detail and described in literature[7-13], oxidative halogenation that showed itself well in the cases with different types of arenes[14] has not been used for this purpose.

To obtain halogenated (-)-cytisine derivatives - the important intermediates in the synthesis of new nAChR ligands, we investigate possibility of halogen introduction into 2-piridone core by reaction of oxidative halogenation in acidic medium[14-17].

EXPERIMENTAL

The oxidative halogenations procedures were carried out in 20-mL glass reactor equipped with thermometer, air condenser and magnetic stirrer (BIOSAN, MSH-300, Latvian republic). Hydrogen

peroxide [CAS 7722-84-1], sulfuric acid [CAS 7664-93-9], hydrochloric acid [CAS 7647-01-0], acetic acid [CAS 64-19-7], potassium chloride [CAS 7447-40-7], potassium bromide [CAS 7758-02-3], potassium iodide [CAS 7681-11-0], sodium carbonate [CAS 497-19-8], sodium sulfate [CAS 7757-82-6], sodium thiosulfate [CAS 7772-98-7] and ethyl acetate [CAS 141-78-6] are commercially available reagents. N-Methylcytisine was obtained by wellknown method[18].

The general procedure of oxidative halogenation of N-methylcytisine with potassium halogenides: 3 mmoles of 30% hydrogen peroxide was added slowly to solution of 1 mmole of compound **(1)** and **(2)** mmoles of potassium halogenide in 5 ml of acid. The solution was stirred at room temperature during 12 hours, after that crystalline Na_2CO_3 was added carefully. After neutralisation has been completed the mixture was extracted with EtOAc. The combined organic layer was washed with solution of $Na_2S_2O_3$, dried with anhydrous Na_2SO_4 and concentrated. The products were isolated by column chromatography (CC) on SiO_2.

CC was carried out on standard silica gel 60 (0.05–0.1 mm, MACHEREY-NAGEL, Germany) with ethyl acetate as the eluent; the thin-layer chromatography (TLC) was carried out using ALUGRAM® pre-coated aluminium sheets with 0.20 mm silica gel 60 with fluorescent indicator UV_{254}.

NMR spectra were recorded in $CDCl_3$ solution on a Bruker AVANCE-III 500 spectrometer (5mm z-gradient PABBO) operating at 500.30 MHz (^1H) and 125.75 MHz (^{13}C).

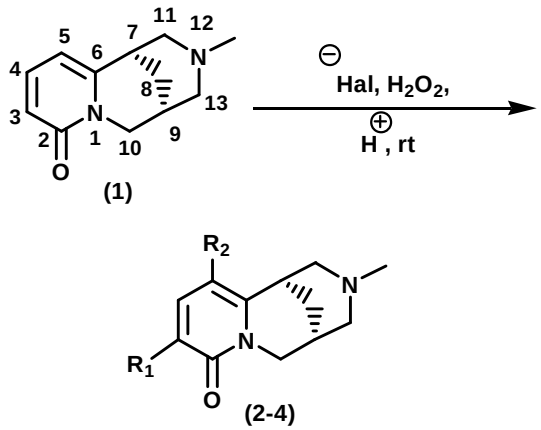
The ratio of regioisomers were determined by integration of uniquely characteristic signals in ^1H NMR spectra of crude reaction mixture. Structures elucidation and ^1H, ^{13}C NMR signals assignments were performed using COSY, NOESY, HSQC and HMBC experiments. Assignments of 3- and 5-monohalogenated compounds **(2-4) (a,b)** were carried out on the basis NOESY data. In the case of 3-halogenated derivatives H-5 protons are NOESY coupled with H-7.

Melting points of crystalline products were determined using Boetius apparatus (PHMK 05 VEB Wagetechnik Rapido, Radebeul). Optical rotation were measured on Perkin Elmer 341 LC digital polarimeter (sodium lamp, 589 nm wavelength). High-resolution mass-spectra were recorded by Thermo Finnigan MAT95XP mass-spectrometer (EI, 70 eV).

Physical constants and NMR spectral characteristics of the compounds are in accordance with the literary data[7,8,13].

RESULTS AND DISCUSSION

In this paper we represent the first example of oxidative halogenation of 2-pyridone core of N-methylcytisine **(1)** by system "halogenide - hydrogen peroxide in acidic medium" (Scheme 1). As halogenide donors, potassium salts KCl, KBr and KI or hydrochloric acid – HCl were used. 30% Hydrogen peroxide was used as an oxidising agent, and 20%, 50% sulfuric acid or 98% acetic acid as solvents. Reaction conditions and yields of resulting compounds are presented in TABLE 1.



Hal = Cl	Hal = Br
R_1 = Cl , R_2 = H (2a)	R_1 = Br , R_2 = H (3a)
R_1 = H, R_2 = Cl (2b)	R_1 = H, R_2 =Br (3b)
R_1 = Cl, R_2 = Cl (2c)	R_1 = Br, R_2 = Br (3c)

Hal = I
R_1 = I , R_2 = H (4a)
R_1 = H, R_2 =I (4b)
R_1 = I, R_2 = I (4c)

Scheme 1 : Oxidative halogenation of N-methylcytisine.

It is known, that efficiency of oxidative halogenation of arenes is defined by nature of halogen anion, functional groups of the aromatic ring, solvent and some another factors[14]. In the case with N-methylcytisine, the yield of halogenated products strongly depends on the acid concentration: the yield of 5-chloro derivative **(2b)**

increases from 11 to 43%, and the yield of 3,5-dibromo derivative **(3c)** from 85 to 94% if 20% sulfuric acid is replaced by 50% sulfuric acid (entries 1, 2 and 9, 10, TABLE 1).

While acetic acid is used as a solvent the regioselectivity of bromination varies - the yields of compounds **(3a)**, **(3b)** and **(3c)** are 22, 47 and 8%. Chlorination and iodination in acetic acid have been unsuccessful - we could not detect even trace amounts of desirable products (entries 5, 16, TABLE 1).

When chlorination of **(1)** are carried out in concentrated hydrochloric acid (which is, at the same time, both a chloride anion donor and a solvent[16]) using 5-fold excess of hydrogen peroxide, 3,5-dichloro derivative **(2c)** becomes the unique reaction product with a yield of 17% (entry 6, TABLE 1).

A large excesses of reagent (entries 4 and 7, TABLE 1) leads to both an increase in total yield of reaction products and an increase in yield of 3,5-dichloro product **(2c)**.

TABLE 1 : Reaction conditions[a] and yields of halogenated products 2a, b, c-4a, b, c

No.	Reagent, eq.	Solvent	Yields[b], %		
			2a	**2b**	**2c**
1	$2KCl/3H_2O_2$	H_2SO_4 (20%)	-	11	-
2	$2KCl/3H_2O_2$	H_2SO_4 (50%)	-	43	6
3[c]	$2KCl/3H_2O_2$	H_2SO_4 (50%)	-	49	12
4	$4KCl/6H_2O_2$	H_2SO_4 (50%)	-	21	48
5	$2KCl/3H_2O_2$	AcOH (98%)	-	-	-
6	$5H_2O_2$	HCl (37%)	-	-	17
7	$15H_2O_2$	HCl (37%)	-	-	70
			3a	**3b**	**3c**
9	$2KBr/3H_2O_2$	H_2SO_4 (20%)	-	-	85
10	$2KBr/3H_2O_2$	H_2SO_4 (50%)	-	-	94
11	$1KBr/6H_2O_2$	H_2SO_4 (50%)	-	9	24
12	$2KBr/3H_2O_2$	AcOH (98%)	22	47	8
			4a	**4b**	**4c**
13	$2KI/3H_2O_2$	H_2SO_4 (20%)	2	-	-
14	$2KI/3H_2O_2$	H_2SO_4 (50%)	1	-	3
15[d]	$2KI/3H_2O_2$	H_2SO_4 (50%)	10	2	2
16	$2KI/3H_2O_2$	AcOH (98%)	-	-	-

[a]**The reactions were carried out at room temperature for 12 h.**
[b]**Regioisomers ratio was determined on the basis of ^{1}H NMR spectroscopy data.**
[c]**The reaction was carried out at 0°C.**
[d]**The reaction was carried out at 70°C.**

Variation of temperature conditions also influences process efficiency. Thus, decrease of the chlorination reaction temperature to 0°C (entry 3, TABLE 1) allows 5-chloro compound **(2b)** with a yield of 49%, and increase of the temperature to 70°C in the case with iodination leads to noticeable yields (near 10%) of 3-iodo compound **(3a)** (entry 15, TABLE 1).

CONCLUSIONS

In summary, our results are shown that oxidative halogenation of N-methylcytisine in the chosen conditions is inapplicable for iodination but can be used for synthesis of 3,5-dichloro derivative and for successful synthesis of 3,5-dibromo derivative. These facts allow us to recommend this system for chlorination and bromination of quinolizidine alkaloids with 2-pyridone core moiety and for replacement of such aggressive and toxic reagents[7,8] as molecular chlorine and bromine.

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