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Jean-Daniel Andre [a] , Jean-Robert Dormoy [a] & Alain Heymes [a]
[a] Sanofi-Chimie, Route de Gap, BP 15, 04201, Sisteron, Cedex, France

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O-DEMETHYLATION OF OPIOID DERIVATIVES WITH METHANE SULFONIC ACID / METHIONINE : APPLICATION TO THE SYNTHESIS OF NALOXONE AND ANALOGUES.

Jean-Daniel Andre*, Jean-Robert Dormoy, Alain Heymes

Sanofi-Chimie, Route de Gap, BP 15, 04201 Sisteron cedex, France.

Abstract : *Naloxone 2 was obtained by demethylation of N-allylnoroxycodone 1 with methane sulfonic acid / methionine. This reagent is an excellent substitute for boron tribromide. It was used for the synthesis of analogous derivatives with variable results.*

Many active opioid derivatives[1] have an hydroxyl group at the 3 position and their synthesis requires O-demethylation of the intermediate methyl ether. Cleavage of aryl methyl ethers to give phenols is well

* To whom correspondence should be addressed

described[2]; many reagents have been used for the hemisynthesis of morphinans but the results depend on the structure.

Boron tribromide[3] is the reagent most frequently employed as a result of mild conditions together with high yield and selectivity. Potassium hydroxide[4], used for the Diels-Alder adducts of thebaine, and pyridine hydrochloride[5] require more drastic conditions. Diphenyllithium phosphide[6] and, recently, thiolate anions[7] have also been used. In spite of certain advantages, boron tribromide is not convenient at industrial scale owing to toxicity and difficult handling.

We have found a reagent to replace it, particularly for the synthesis of naloxone **2**. This is the methane sulfonic acid - methionine system, known as hard acid - soft nucleophile reacting by a push-pull mechanism[8]. This type of reagent, developped by Yajima[9] and Kiso[10], has been applied to deprotect peptides. Only a few examples of cleavage of aryl methyl ethers have been mentioned and the yields are poor[11].

We report herein a new preparation of naloxone **2** from N-allyl noroxycodone **1** with 30 equivalents of methane sulfonic acid and 1.5 equivalents of methionine over 15 hours at 40°C (scheme **1**).

A large excess of methane sulfonic acid is needed whereas just a slight excess of methionine is

Scheme 1

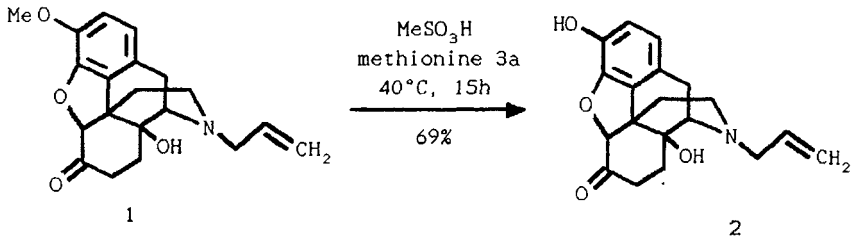


Table 1. Demethylation of N-allyl noroxycodone **1** with $MeSO_3H$ / methionine[a]

Reaction Conditions		Yield (%)[b]	
Time (h)	Temp. (°C)	**2**	**1**
55	20	66	23
15	30	67	17
15	40	69	12
40	40	58	0
14	60	58	1
6	80	46	0

a 30 equivalents $MeSO_3H$ / 1.5 equivalents methionine.

b Determined by HPLC (external standard).

Table 2. Demethylation of N-allyl noroxycodone **1** with strong acid / methionine[a]

Reaction Conditions				Yield (%)[b]	
Acid(equiv)	Solvent	Time(h)	Temp.(°C)	**2**	**1**
$MeSO_3H$ (30)	-	15	40	69	12
CF_3SO_3H (15)	-	6.5	20	59	3
CF_3SO_3H (5)	CF_3CO_2H	29	20	69	5
$ClSO_3H$ (15)	-	1	20	0	0
H_2SO_4,SO_3[c] (15)	-	8	20	0	0
Nafion[d] (30)	$CHCl_3$	30	25-35	0	65

a 1.5 equivalents methionine.

b Determined by HPLC (external standard).

c 20% of SO_3.

d Nafion 117, H^+ form, contains 0.9 mmol RSO_3H/g.

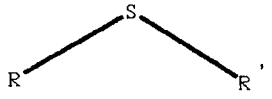
sufficient. Time and temperature have an influence on kinetics and also on degradation which can attain 40% above 60°C. Also, prolonged reaction leads to much degradation, even at 30-40°C (Table 1).

The optimal temperature seems to be 30-40°C and the time should not exceed 15 hours.

A cosolvent such as dichloromethane, trifluoroacetic acid, trifluoromethane sulfonic acid or

pyridine does not improve the results. Methane sulfonic acid can be replaced by trifluoromethane sulfonic acid. The other acids tested are less effective (Table 2).

Among various sulfides used, tetrahydrothiophene and dibutyl sulfide give similar results to those obtained with methionine (Table 3).



3

3	R	R'
a	Me	$CH_2CH_2CH(NH_2)CO_2H$
b	Me	Ph
c	n-Bu	n-Bu
d	Me	t-Bu
e	$-(CH_2)_4-$	
f	H	$CH_2CH_2CH(NH_2)CO_2H,HCl$

Possible side-reactions are :

- Alkylation of tertiary amine **1** or **2** by sulfonium ion resulting from demethylation reaction and formation of quaternary ammonium compound,
- Cleavage of cyclic arylalkyl ether **1** or **2** and formation of sulfonium ion,

Table 3. Demethylation of N-allyl noroxycodone **1** with $MeSO_3H$ / dialkyl sulfide[a]

Reaction conditions			Yield (%)[b]	
Dialkyl sulfide (equiv)	Time(h)	Temp.(°C)	**2**	**1**
Methionine 3a (1.5)	15	40	69	12
3b (3)	32	20-60	12	3
3c (1.5)	27	20-60	59	10
3d (1.5)	16	20-60	0.5	5
3e (1.5)	20	40	62	16
3f (1.5)	6.5	20	0	0

a 30 equivalents $MeSO_3H$.

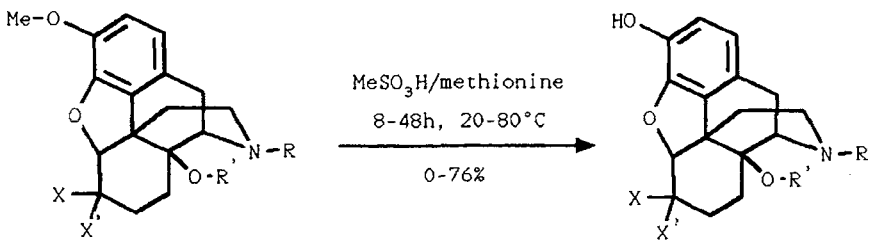
b Determined by HPLC (external standard).

- Alkylation of sulfide **3a** with tertiary alcohol **1** or **2** and formation of sulfonium ion[12].

All these by-products are soluble in water and easily eliminated. Not all have been fully characterized.

Our demethylation conditions, methane sulfonic acid / methionine, have been applied to various intermediates in the synthesis of naloxone (Scheme **2** and Table 4). Oxymorphone **5a** is obtained in 76% yield. In the case of oxycodone acetate **4b**, hydrolysis of acetate leads to oxymorphone **5a**.

Scheme 2



4 5

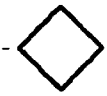
4,5	R	R'	X,X'
a	Me	H	= O
b	Me	Ac	= O
c	H	H	= O
d	CO_2Et	H	= O
e	CH2- 	H	= O
f	CH2- 	H	H,OH
g	CH2- 	H	= CH_2

Table 4. Demethylation of **4a-g** with $MeSO_3H$/methionine[a]

4	Reaction Conditions		5	Yield[b] (%)	Litterature		
	Time(h)	Temp.(°C)			Ref	Yield(%)	Method[c]
4a	12	40	5a	76	13	27	A
					5	69	B
					14	76	C
4b	19	20-40	5a	59	13	d	
4c	14	40-80	5c	0	15	e	C
4d	48	20	5d	18	16	73	C
4e	8	40	5e	65	17	73	B
4f	8	40	5f	47	18	69	C
4g	24	40	5g	mixt.	19	f	

a 30 equivalents $MeSO_3H$ / 1,5 equivalents methionine.

b Determined by HPLC (external standard).

c A: HBr/reflux; B: Pyridine,HCl/200°C; C: BBr_3.

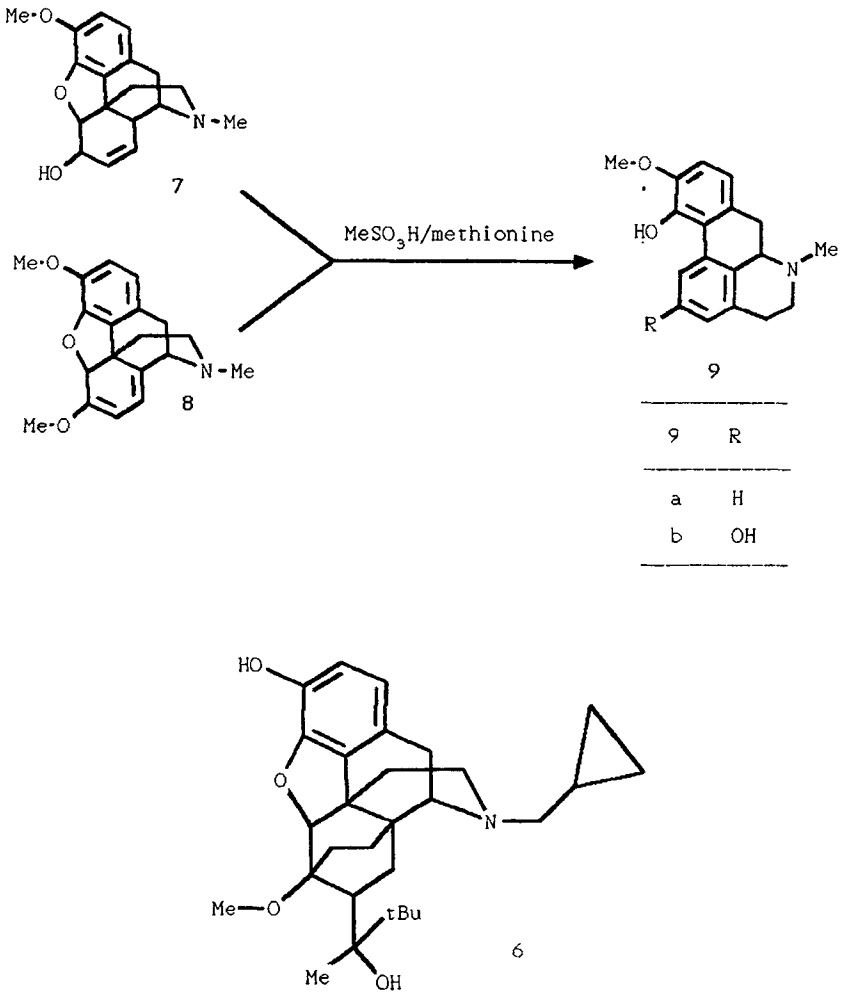
d Obtained by demethylation of 5a.

e Not indicated.

f Obtained by a Wittig reaction with naltrexone.

Demethylation of analogous derivatives to obtain naltrexone **5e**, nalbuphine **5f** and nalmetrene **5g** has been

Scheme 3



carried out with varying results (Table 4). Buprenorphine **6** was not obtained under these conditions, the tertiobutyl group being acid-labile.

Codeine **7** and thebaine **8** undergo rearrangement to **9a** and **9b** respectively (Scheme **3**). This reaction is known with methane sulfonic acid alone[20].

Until now, this new method of demethylation of ethers was essentially used to deprotect peptides. We have advantageously applied it to the preparation of opiod alkaloids[21]. Reagents are easily handled and can be used at industrial scale.

EXPERIMENTAL

98% $MeSO_3H$ and DL-methionine were purchased from Janssen Chimica. Ammonium hydroxyde contains 21% of NH_3. Alumina CBT2 was purchased from Rhone Poulenc. Reagent grade solvents were used without further purification. Melting points were taken using a Tottoli apparatus (Buchi) and are uncorrected. Optical rotations at the Na-D line were obtained at ambient temperature using a Perkin-Elmer 241 polarimeter. ^{1}H-NMR spectra were obtained using a Brucker 300 MHz spectrometer. HPLC were performed on a C_{18} μbondapack column; mobile phase: MeOH 50 / 0.1% aqueous $(NH_4)_2CO_3.7H_2O$ 50; detector UV at 240 nm; flow rate: 2mL/min.

N-allyl-7,8-dihydro-14-hydroxynormorphinone or naloxone (2):

DL-methionine (**3a**; 22.4g, 0.15mol) is added over 15 min at 40°C to a stirred solution of N-allyl-noroxycodone (**1**; 34.12g, 0.1mol) in $MeSO_3H$ (288g, 3mol) and stirring

is continued at 40°C for 15h. After cooling to room temperature, the mixture is slowly poured into NH_4OH (300mL) and ice (300g) and extracted with AcOEt (5 X 400mL). The organic layers are washed with water (400mL), dried (Na_2SO_4) and the solvent removed under reduced pressure. The residue (30.7g) is taken up in chloroform (600mL) and stirred with alumina CBT2 (86g) during 10 min. The suspension is filtered and the filtrate evaporated. The crude product is crystallized from toluene (600mL) to give naloxone **2**; yield: 19.8g (60%); mp 179.5°C; $[\alpha]_D^{22}$ -215° (c=1, MeOH) (Lit.[22] mp 177-178°C). ^{1}H-NMR ($CDCl_3$-DMSO): δ= 1.5-3.3 (m,13H), 4.7 (s, 1H, CHO), 5.2 (m, 2H allyl), 5.5 (s, 2H, 2OH), 5.8 (m, 1H allyl), 6.6 (d, 1H, J=8, H arom), 6.7 (d, 1H, J=8, H arom).

Hydrochloride: a solution of purified product (**2**; 5g, 15.2mmol) in acetone (30mL) is concentrated to 10mL and HCl 6N (5mL, 30mmol) added at 50°C. The hydrochloride crystallizes at -10°C. Yield: 4.83g (87%); assay 99.9% (HPLC); $[\alpha]_D^{22}$ -179° (c=2.5, H_2O).

O-Demethylation of 4a-g with $MeSO_3H$ / methionine; General Procedure:

DL-methionine (**3a**; 0.75g, 5 mmol) is added at 40°C to a solution of **4a-g** (3.3 mmol) in $MeSO_3H$ (9.6g, 100 mmol) and stirring continued. Time and temperature are given in Table 4. The mixture is cooled to r.t. and poured into NH_4OH (10mL) and ice (10g). The crude product **5a-g**

is obtained after extraction with AcOEt (5 X 20mL). Yields are determined by HPLC (Table 4).

^{1}H-NMR ($CDCl_3$-DMSO) δ/TMS, J(Hz):

5a: 1.5-3.25(m,11H), 2.4(s,3H,NCH_3), 4.7(s,1H,CHO), 4.8(s,2H,2OH), 6.6(d,1H,,J=8,H arom), 6.7(d,1H,J=8,H arom).

5d: 0.9-3.3(m,11H), 1.25(t,3H,J=6,CO_2Et), 4.1(q,2H,J=6, CO_2Et), 4.7(s,1H,CHO), 5-6(m,2H,2OH), 6.65(d,1H,J=8,H arom), 6.75(d,1H,J=8,H arom).

5e hydrochloride: 0.35-1.2(m,5H,cycloPr), 1.4-3.5(m, 12H), 4(m,1H,CHN), 5(s,1H,CHO), 6.6(d,1H,J=8,H arom), 6.7(d,1H,J=8,H arom), 6.95, 9.05 and 9.5(3s,3H,2OH, NH^+).

5f hydrochloride: 0.9-3.5(m,20H), 4.1(m,1H,CHOH), 4.5 (d,1H,J=4,CHO), 4.65(d,1H,J=5,CHOH), 6.25(s,1H,14-OH), 6.5(d,1H,J=8,H arom), 6.65(d,1H,J=8,H arom), 8.7(s,1H, NH^+), 9.15(s,1H,OH arom).

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