Tetrahedron Letters,Vol.30,No.13,pp 1633-1636,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

AN EASY ROUTE TO BENZOPYRROLIZINES RELATED TO MITOMYCIN A VIA CHROMIUM CARBENE COMPLEXES [1]

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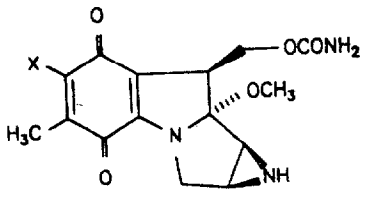
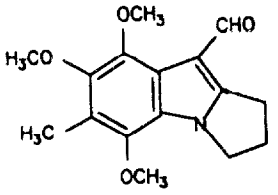
SUMMARY: Benzopyrrolizines 5 and 7 have been obtained by reaction of the dihydropyrrolizidine chromium(0)carbene complexes 4 and 6 with acetylenes. The regiochemistry of the cycloaddition of alkoxypropynes could be reversed leading for the first time to a trimethylsilyl-benzopyrrolizine 5d with a substitution pattern necessary for subsequent synthesis of mitomycin A.

The construction of benzene derivatives with a substitution pattern related to mitomycins required a laborious low yield multistep route in the synthesis of mitomycin A 1 [2] as well as mitosanes [3], mitosenes [4] and more simple indole derivatives [5]. Recently, we reported a 13 step synthesis of the mitosane derivative 2 with a total yield of 2.5% [6].



1 X = OCH_3



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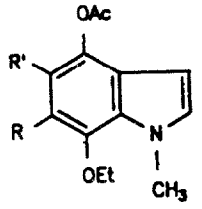
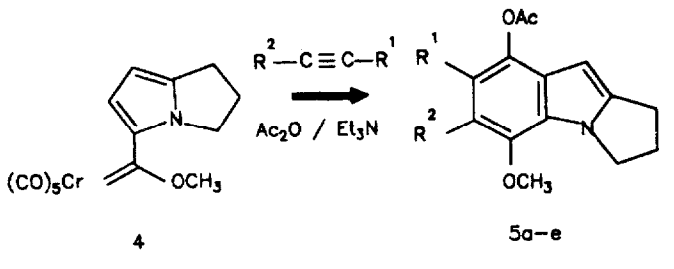


3

In our search for a shorter and more efficient way to suitably substituted mitosene derivatives [1] we investigated the Dötz reaction [7] using a modified method of functionalization of the addition product which has been shown recently to give indole derivatives 3 starting from N-methylpyrrole [8].

A reaction of the carbene complex 4 obtained in 67% yield in the usual way [7], however, gave only the wrong regioisomers 5a/b [9,10] upon reaction with alkoxypropynes as shown by NOE experiments.

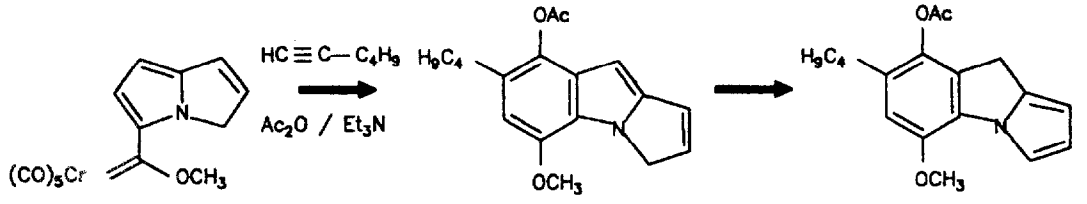


4 5a–e

	R^1	R^2
a	CH_3	OCH_3
b	CH_3	OC_2H_5
c	$n\text{-}C_4H_9$	H
d	$Si(CH_3)_3$	CH_3
e	CH_3	$Si(CH_3)_3$

The regioselectivity of the addition of acetylenes to the carbene complex 4 may be controlled by steric and/or electronic effects. From a reaction with 1-hexyne only 5c [10] was obtained indicating a determinating steric influence on the reaction. This would explain the course of formation of benzopyrrolizines 5a/b since the methyl group (E_S=0.00[11]) is more bulky than the methoxy group (E_S= +0.99[11]).

A reaction of 4 with 1-trimethylsilylpropyne gave besides small amounts of 5e mainly the benzopyrrolizine derivative 5d [10] with the desired substitution pattern. This has been proven unequivocally by NOE mesurements. Unoptimized experiments resulted in a yield of 32% of pure 5d rendering our new method superior to any of the previously reported [2-6]. The easily convertible trimethylsilyl group, moreover, paves the way to various 7-functionalized benzopyrrolizines not accessible so far [12].



6 7a 7b

Apart from dihydro derivatives even 3H-pyrrolizines are amenable to the Dötz reaction, which may be useful for the synthesis of 1.2-functionalized benzopyrrolizines.

From the anion of 3H-pyrrolizine [13] 42% of the carbene complex 6 have been obtained by the procedure described already [7]. Only one of two

possible 3H-tautomers was formed [10] due to the electron withdrawing character of the carbene functionality [14]. A first informal reaction of 6 with 1-hexyne gave 18% of the 9H-benzopyrrolizine 7b [10] obviously formed via the more unstable tautomer 7a [15].

ACKNOWLEDGEMENT

Financial support of these investigations by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged. We are indebted to Prof. K.-H. Dötz for helpful advice and discussions.

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7) K.-H. Dötz, Angew.Chem. 96,(1984),573; ibid.Int.Ed.Engl. 23,(1984),587. 4-Lithio-1.2-dihydro-3H-pyrrolizine, generated from 1.2-dihydro-3H-pyrrolizine and tert.butyl lithium in THF at -78°C, was treated with $Cr(CO)_6$ at room temperature and subsequently methylated with Meerwein salt. Chromatography (silica gel; pentane/dichlormethane = 2/1) gave 62% 4.
8) A. Yamashita, T.A. Scahill and C.G. Chidester, Tetrahedron Lett. 26,(1985),1159; A. Yamashita, T.A.Scahill and a. Toy, ibid. 26,(1985),2969.
9) 3.1 mmol 4, 12.4 mmol 1-hexyne, 3.2 mmol acetic anhydride and 3.2 mmol triethylamine in 30 ml deoxygenated THF stirred under argon at 70°C for 6 hours. The benzopyrrolizine 5c was isolated by flash chromatography on silica gel in 22% yield.
10) New compounds were characterized by elemental analysis and spectra. ^1H NMR data (acetone-d_6): 5b δ 5.85(t,$J_{9,1}$=0.8Hz,C-9 1H); 4.01(q,OCH_2CH_3), 3.93(s,OCH_3); 2.86(m,$J_{1,9}$=0,8Hz,C-1 2H; 2.56(m,C-2 2H); 2.27(s,$ArCH_3$);

2.08 (s,$OCOCH_3$); 1.37(t,$OCH_2C\underline{\underline{H}}_3$). 5d δ 5.81(t,$J_{9,1}$=0.8Hz,C-9 1H); 4.25(m,C-3 2H); 3.79(s,OCH_3); 2.89(m,$J_{1,9}$=0.8Hz,C-1 2H); 2.58(m,C-2 2H); 2.42(s,$ArCH_3$); 2.31(s,$OCOCH_3$); 0.35(s,$Si(CH_3)_3$). Solvent benzene-d6: 6 δ 3.25(t,$J_{3,2}$=1.5Hz,C-3 2H); 4.02(s,OCH_3); 5.63(d,$J_{7,6}$=4.5Hz,C-7 1H); 5.88(m,C-1 1H); 5.90(m,C-2 1H); 7.86(d,$J_{q6,7}$=4.5Hz,C-6 1H). 7b δ 0.95(t,$Ar-CH_2-CH_2-CH_2-C\underline{\underline{H}}_3$); 1.35(m,$Ar-CH_2-CH_2-C\underline{\underline{H}}_2-CH_3$); 1.58(m,$Ar-CH_2-C\underline{\underline{H}}_2-CH_2-CH_3$); 1.83(s,$OCOCH_3$); 2.51(t,$Ar-CH_2-$); 3.51(d,C-9 2H); 3.54(s,OCH_3); 6.17(m,C-1 1H); 6.46(s,C-6 1H); 6.56(dd,C-2 1H); 7.63(d,C-2 1H).

Steady state NOE difference spectra of 5d (360 MHz, 10 mM solution in acetone-d_6, 24°C. Saturation > 90%. Estimated error +/- 0.5%)

Nuclear Overhauser enhancements (%)

	OCH3	CH3(6)	SiMe3	OAc(8)	C(9)H	C(3)H2
OCH3		2.3	0	0	0	1.9
CH3(6)	1.5		1.0	0	0	0
SiMe3	0	2.7		1.5	0	0
OAc(8)	0	0	1.3		4.0	0

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(Received in Germany 20 January 1989)