Tetrahedron Letters,Vol.30,No.26,pp 3423-3426,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Maxwell Pergamon Macmillan plc

GENERATION OF β-CARBOLINE AZOMETHINE YLIDES VIA TRIMETHYLSILYLMETHYL TRIFLUOROMETHANE SULFONATE QUATERNISATIONS: ENTRY INTO THE NEW CLASS OF 11H-INDOLIZINO[8,7-b]INDOLE HETEROCYCLES

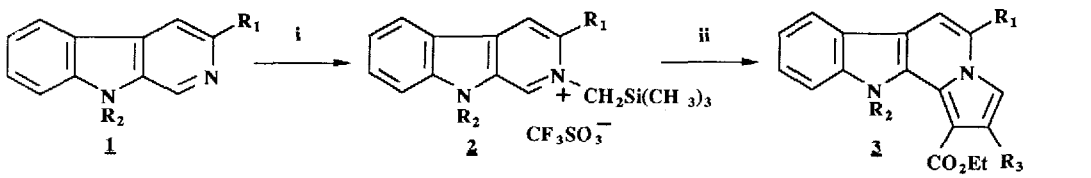
Guillaume Poissonnet, Pierre Potier, and Robert H. Dodd*
Institut de Chimie des Substances Naturelles, C.N.R.S., 91198 Gif-sur-Yvette, France

Summary: Norharman (**1a**), ethyl N-tosyl-β-carboline-3-carboxylate (**1b**) and N-benzyl-3,4-dihydronorharman (**4**) were quaternised with trimethylsilylmethyl trifluoromethane sulfonate and the corresponding azomethine ylides were generated with caesium fluoride; 1,3-dipolar cycloaddition of these ylides with diethyl acetylene dicarboxylate yielded the first known examples of 11*H*-indolizino[8,7-*b*]indoles.

Several β-carboline congeners in which a six-membered aromatic ring is fused to the 1,2 position (*e.g.* semperverin) are known to display anticancer activity[1]. In connection with our programme of new anticancer drug development, we were interested in preparing various tetracyclic β-carbolines such as (3) in which a five-(rather than a six-)membered ring is fused to the 1,2 position of the β-carboline. The use of [3+2] cycloadditions to non-stabilized ylides[2] generated from hitherto unknown α-trimethylsilyl iminium salts of β-carboline appeared to be a convenient entry to this new class of compounds. Herein we report preliminary results of our studies.

Alkylation of the β-carboline norharman (**1a**) with trimethylsilylmethyl trifluoromethane sulfonate (triflate) in dichloromethane (CH_2Cl_2) at room temperature occurred regiospecifically at the N-2 position in a few hours to give (**2a**) [3]. The non-stabilized azomethine ylide was then generated from (**2a**) by treatment with caesium fluoride in dimethoxyethane (DME) at reflux[4] and trapped with the acetylenics diethyl acetylene dicarboxylate (DEAD) and ethyl propiolate to give (**3a**) and (**3c**), respectively. The formation of the single regioisomer (**3c**) was indicated by its 400 MHz ^1H n.m.r. spectrum which exhibits an AB quartet centred at 7.30 ppm (J = 3 Hz)[5].This regiospecificity may be explained by the formation of a hydrogen bond between the indolic N-H and the carbonyl group of ethyl propiolate thereby stabilizing the adduct which leads to exclusive formation of (**3c**).

This procedure was extended to the pharmacologically important ethyl ester of β-carboline-3-carboxylic acid(**1b**, R_2=H, β-CCE)[6]. In contrast to (**1a**), however, the presence of the carboxylate group in β-CCE induced resistance to alkylation at the pyridine nitrogen[7] by the triflate, necessitating protection of the indolic N-H (as its tosylate, **1b**) to avoid its competing alkylation. Moreover, (**2b**)was obtained as a mixture of silylated compound and unreacted (**1b**), but could be used without purification in further steps. Thus , the ylide generated , as before , from (**2b**)was trapped with DEAD to give (**3b**).



1a $R_1=R_2=H$
1b $R_1=CO_2Et : R_2=p\text{-}MeC_6H_4SO_2$

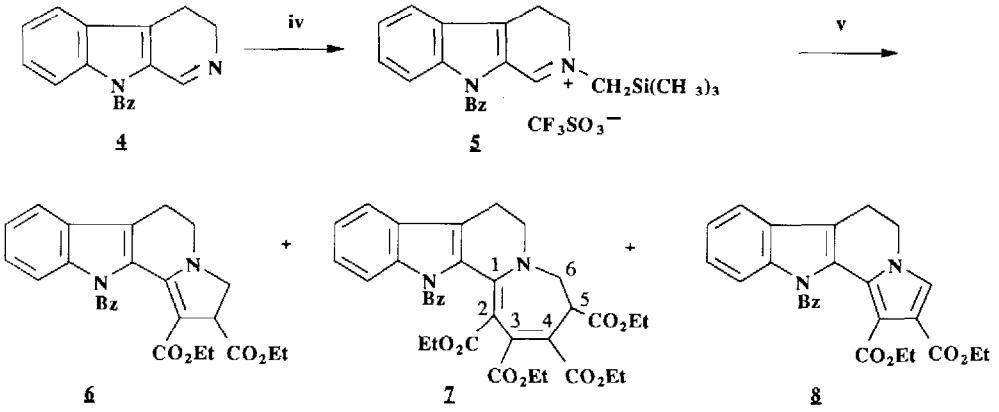
2a $R_1=R_2=H$
2b $R_1=CO_2Et : R_2=p\text{-}MeC_6H_4SO_2$

3a $R_1=R_2=H : R_3=CO_2Et$
3b $R_1=CO_2Et : R_2=p\text{-}MeC_6H_4SO_2$
3c $R_1=R_2=R_3=H$
3d $R_1=R_3=CO_2Et : R_2=H$

i, $(CH_3)_3SiCH_2OSO_2CF_3$, CH_2Cl_2, 25°C, [(1a)-100%]; ii, CsF, DME reflux, $R_3C{=}CCO_2Et$, [(3a)-35%, (3b)-18% from (1b) and (3c)-8%]; iii, NaH, EtOH, THF, 0°C, [(3d)-100%].

Quantitative N-detosylation of (3b) could be achieved in tetrahydrofuran at 0°C with one equivalent of sodium ethanolate to give (3d).

Application of the method to 3,4-dihydro-β-carbolines allowed entry into the tetrahydro-β-carboline series of tetracyclic derivatives. The iminium salt (5) was obtained in good yield (83%) by treatment of (4) with trimethylsilylmethyl triflate and the ylide generated from (5) was trapped with DEAD to give three products. In contrast to the product obtained with the completely aromatic (1a), only small quantities of the analogous dehydrogenated derivative (8) were observed, the major product being the 1:1 adduct (6). A more important by-product in this reaction was the 1:2 adduct (7). The formation of



iv, $(CH_3)_3SiCH_2OSO_2CF_3$, CH_2Cl_2, 25°C, 83%; v, CsF, DEAD, DME (for the yield, time and temperature see table 1).

this compound may be explained by an initial addition of one molecule of DEAD to the ylide followed by reaction of the resulting transitory intermediate with another molecule of DEAD before the cyclisation is achieved. A [1,5] hydrogen shift then leads to (7). The structure of the latter was suggested by its 400 MHz ^{1}H n.m.r spectrum which displays two quadruplets at δ = 2.49 ppm and δ = 3.22 ppm for the two H_6 protons (JH_6-H_6 = 13 Hz and JH_6-H_5 = 11 Hz)[8]. The complete assignment of the signals by two-dimensional carbon-proton shift correlation n.m.r. unambiguously confirmed the structure of (7). When compound (6) was refluxed in DME in the presence of caesium fluoride and DEAD, no (7), even in trace amounts, could be observed thereby indicating that the latter compound was not formed *via* a 1,3-dipolar cycloreversion reaction [9]

Table 1. Effect of temperature and concentration on the product distribution of the cycloaddition reaction between (**5**) and DEAD.

		Yield (%)		
Temp.°C	Time h	(**6**)	(**7**)	(**8**)
80	1	43	40	8
0	3	47	29	3
-44	6	58	30	10
-44[a]	22	54	14	9

[a] : Triflate (**5**) concentration : 5.10^{-4} mole/l.

The formation of (7) was minimised but not prevented by conducting the reaction at -44°C (see table 1). Moreover, running the reaction in dilute solution [*i.e.* 5.10^{-4}mole/liter in salt (5)] also decreased the formation of the 1:2 adduct though not in favour of 1:1 cycloadduct formation (table 1).
Thus, 1,3-dipolar cycloaddition reactions to β-carboline azomethine ylides allow access to the novel class of 11*H*-indolizino[8,7-*b*]indoles. This procedure is currently being applied to the synthesis of biologically targetted β-carboline derivatives.

Acknowledgment. We are grateful to Professor A. Kende and Dr. D. Grierson for valuable discussions.

REFERENCES AND NOTES

1 M. Beljanski and M.S. Beljanski, *Oncology*, 1986, **43**, 198

2 E. Vedejs and F. G. West, *Chem. Rev.*, 1986, **86**, 941

3 All the compounds, except (2b), were fully characterised by u.v., i.r., m.s., and ^{1}H n.m.r. spectra and elemental analysis.

4 O. Tsuge, S. Kanemasa, S. Kuraoka and S. Takenaka, *Chem. Lett.*, 1984, 279

5 A. Padwa, G. Haffmanns and M. Tomas, *J. Org. Chem.*, 1984, **49**, 3314

6 C. Braestrup, M. Nielsen and C. E. Olsen, *Proc. Natl. Acad. Sci. U.S.A.*, 1980, **77**, 2288

7 R. H. Dodd, G. Poissonnet and P. Potier, *Heterocycles*, 1989, 29, 365

8 ^{1}H n.m.r. of compound (7): δ_H(400 MHz; solvent $CDCl_3$; standard Me_4Si) 1.22 (9H, m, $3CH_3$), 1.31 (3H, t, J=8 Hz, CH_3), 2.49 (1H, q, J=13 Hz and J=11 Hz, H_6), 2.85 (1H, septuplet,H_8), 3.11 (1H, septuplet, H_8), 3.21 (1H, q, J=13 Hz and J=11 Hz, H_6), 3.26 (1H, septuplet, H_7), 3.35 (1H, septuplet, H_7), 4.05 to 4.38 (9H, m, $4CH_2$ and H_5), 5.93 (2H, q, J=16 Hz, CH_2 benzylic), 6.96 to 7.13 (6H, m, 5H benzyl and H_{10} or H_{11}), 7.23 (1H, t, J=8 Hz, H_{10} or H_{11}), 7.44 (1H, d, J=8 Hz, H_9), 7.58 (1H, d, J=8 Hz, H_{12}). U.V. λ max.nm (Log ε): 354,0 (3,931), 324,4 (3,943), 237,7 (4,020), 208,4 (4,236). I.R. ν cm^{-1}: 2950,1740,1660,1590. M.S. (EI): 614, 569, 541, 314, 91.

9 G. Bianchi and R. Gandolfi in " 1,3-Dipolar Cycloaddition Chemistry ", ed. A. Padwa, Wiley, New-York, 1984, Vol. 2, p. 500.

(Received in France 4 April 1989)