

A NEW ENTRY TO [2.3.4]CYCLAZINES

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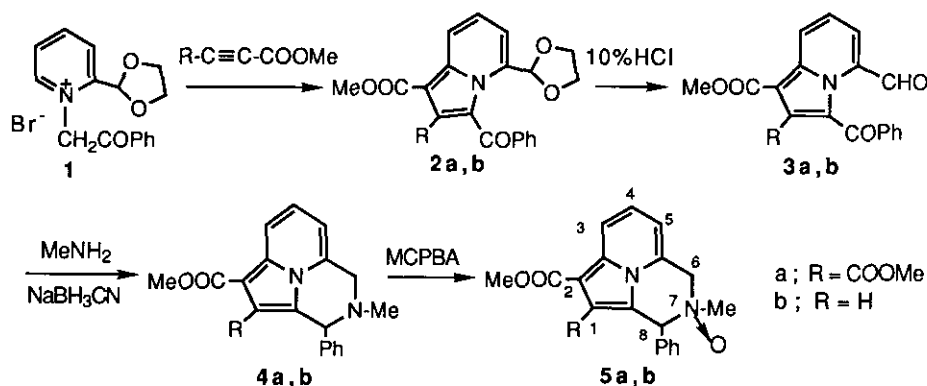
Abstract — Treatment of 2,3-dihydro-2-methyl-3-phenyl-1*H*-pyrazino[3,4,5-*cd*]indolizine 2-oxides (5) with trifluoroacetic anhydride gave new heterocyclic six-membered betaines (6) which underwent 1,3-dipolar cycloaddition reaction with dimethyl acetylenedicarboxylate and maleimides in hot toluene to yield the corresponding cycloadducts (7) and (8). Treatment of the maleimide adducts (8) with *p*-toluenesulfonic acid in boiling acetic acid gave the [2.3.4]cyclazines (9).

[2.3.4]Cyclazines,¹ characterized as *N*-bridged [12]annulenes, were first synthesized in 1973 by cyclization of diethyl (4-oxo-4*H*-3*a*-aza-3-azulenylmethylene)succinate² and later by ring-opening of cyclobuta[*a*][2.2.3]cyclazines.³ In this communication we report a new entry to the [2.3.4]cyclazines (9) which involves a 1,3-dipolar cycloaddition of maleimides to the betaines (6) followed by acid treatment of the cycloadducts (8).⁴

Reaction of 1-phenacyl-2-(1,3-dioxolan-2-yl)pyridinium bromide (1), prepared from 2-(1,3-dioxolan-2-yl)pyridine⁵ and phenacyl bromide in boiling acetonitrile in 90% yield, with dimethyl acetylenedicarboxylate or methyl propiolate in the presence of potassium carbonate in tetrahydrofuran at room temperature gave methyl 3-benzoyl-5-(1,3-dioxolan-2-yl)indolizine-1-carboxylates (2)(a; 59%, b; 52%). The

indolizines (**2a,b**) were deprotected with 10% hydrochloric acid to afford the aldehydes (**3a,b**) (a; 92%, b; 92%). The aldehydes (**3a,b**) were converted by reductive amination with methylamine and sodium cyanoborohydride in methanol into the tricyclic amines (**4a,b**) which were, without purification, led to the corresponding *N*-oxides (**5a,b**) (a; 58%, b; 73%) by *m*-chloroperbenzoic acid oxidation (in CH_2Cl_2 , 0°C , 10-20 min)(Scheme 1).

Scheme 1



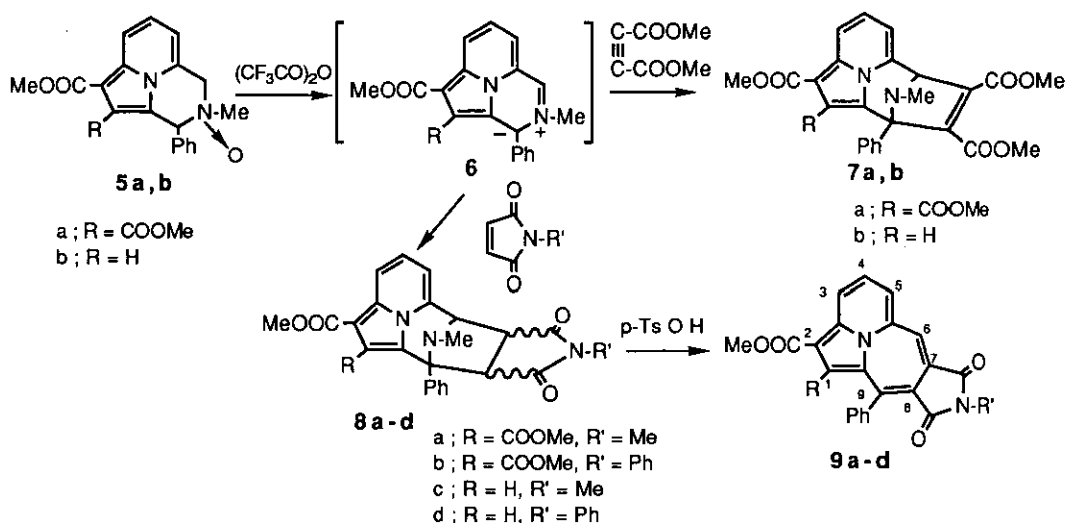
Treatment of the *N*-oxides (**5a,b**) with trifluoroacetic anhydride in dichloromethane at 0°C gave a purple solution, implying the formation of the betaines (**6**).⁴ The formation of **6** was further confirmed by trapping **6** with dimethyl acetylenedicarboxylate. Thus, after a solution of dimethyl acetylenedicarboxylate in toluene was added to the purple solution of the betaines (**6a,b**), dichloromethane was evaporated off by heating the reaction mixture under argon and the toluene solution was refluxed for 1 h to afford the corresponding adducts (**7**)(a; 53%, b; 33%). Similar treatment of **5a,b** with *N*-methyl- or *N*-phenylmaleimide yielded the corresponding adducts (**8a-d**) as a mixture of *exo* and *endo* isomers, which was separated by silica gel column chromatography.^{6,7} These results were summarized in Table 1.

In order to convert the adducts (**8**) into the [2.3.4]cyclazine derivatives (**9**), *N*-methylation of **8a** with methyl iodide or methyl trifluoromethanesulfonate under several conditions was attempted without success.⁴ However, treatment of **8a** (as a mixture of the *exo* and *endo* isomers) with 3 molar equivalents of *p*-toluenesulfonic

acid in boiling acetic acid gave directly the desired [2.3.4]cyclazines (**9a**) in 43% yield. Similar treatment of **8b-d** gave the corresponding [2.3.4]cyclazines (**9b-d**) in the yields as shown in Table 2. The structures of the [2.3.4]cyclazines (**9**) were deduced from the spectroscopic evidence.⁸ Of particular interest is that the six-membered ring proton signals of **9a** are shifted *ca.* 1 ppm to higher field than those of either the *exo*- or *endo*-adduct (**8a**). Such higher field shift is characteristic of the [2.3.4]cyclazine ring system.^{2,3} Further discussion of the spectra will be presented in a future publication.

In summary, we have found a new route to the [2.3.4]cyclazines based on the 1,3-dipolar cycloaddition reaction of the six-membered betaines (**6**).

Scheme 2

Table 1. 1,3-Dipolar cycloaddition of **6** with maleimides

8	R	R'	Yield(%)	(<i>exo</i> : <i>endo</i>)
a	COOMe	Me	53	(9.5 : 1)
b	COOMe	Ph	42	(13 : 1)
c	H	Me	48	(15 : 1)
d	H	Ph	36	(11 : 1)

Table 2. Preparation of the [2.3.4]cyclazines (**9**)

9	R	R'	Yield(%)
a	COOMe	Me	43
b	COOMe	Ph	37
c	H	Me	82
d	H	Ph	81

REFERENCES AND NOTES

1. For reviews, see: W. Flitsch, "Comprehensive Heterocyclic Chemistry", ed. A. R. Katritzky and C. W. Rees, Pergamon Press, Vol. 4, p. 478 (1984); W. Flitsch and U. Krämer, *Adv. Heterocycl. Chem.*, 1978, **22**, 321; K. Matsumoto, T. Uchida, and J. Yamauchi, *J. Syn. Org. Chem. Japan*, 1977, **35**, 739.
2. W. Flitsch and B. Mütter, *Angew. Chem.*, 1973, **85**, 543; W. Flitsch, A. Gurke, and B. Mütter, *Chem. Ber.*, 1975, **108**, 2969.
3. V. Batroff and W. Flitsch, *Liebigs Ann. Chem.*, 1987, 621.
4. M. Ikeda, Y. Miki, S. Kaita, Y. Nishikawa, and Y. Tamura, *J. Chem. Soc., Perkin Trans. 1*, 1977, 44; Y. Miki, O. Tomii, M. Utsunomiya, S. Takemura, and M. Ikeda, *Chem. Pharm. Bull.*, 1986, **34**, 3588.
5. C. K. Bradsher and J. C. Parham, *J. Org. Chem.*, 1963, **28**, 83.
6. Both the *exo*- and *endo*-adducts (**8a**) were stable and unchanged after refluxing in toluene for 1 h.
7. **endo-8a**: mp 204-205°C (from methanol); ir (v, cm⁻¹, nujol) 1675, 1710, 1740, and 1785; ¹H-nmr (δ, ppm, 200 MHz, CDCl₃) 2.31 (3H, s, N-Me), 2.49 (3H, s, N-Me), 3.27 and 3.73 (2 x 3H, 2 x s, 2 x COOMe), 4.13 (1H, dd, J=10, 8 Hz, H-7), 4.39 (1H, d, J=10 Hz, H-8), 4.66 (1H, d, J=8 Hz, H-6), 6.62 (1H, br d, J=7 Hz, H-5), 7.05 (1H, dd, J=9, 7 Hz, H-4), 7.3-7.8 (5H, m, Ph), and 7.91 (1H, dd, J=9, 1 Hz, H-3).
exo-8a: mp 239-240°C (dec.)(from methanol); ir (v, cm⁻¹, nujol) 1685, 1735 and 1780; ¹H-nmr (δ, ppm, 200 MHz, CDCl₃) 2.09 (3H, s, N-Me), 2.75 (3H, s, N-Me), 3.41 (1H, d, J=8 Hz, H-7), 3.55 (3H, s, COOMe), 3.75 (1H, d, J=8 Hz, H-8), 3.83 (3H, s, COOMe), 4.74 (1H, s, H-6), 6.79 (1H, dd, J=7, 1 Hz, H-5), 7.14 (1H, dd, J=9, 7 Hz, H-4), 7.3-7.7 (5H, m, Ph), and 8.05 (1H, dd, J=9, 1 Hz, H-3).
8. **9a**: mp above 250°C (from benzene); ir (v, cm⁻¹, CHCl₃) 1670, 1700, and 1745; ¹H-nmr (δ, ppm, 200 MHz, CDCl₃) 2.75 (3H, s, N-Me), 3.05 and 3.55 (2 x 3H, 2 x s, 2 x COOMe), 5.15 (1H, dd, J=7, 1 Hz, H-5), 5.22 (1H, s, H-6), 5.98 (1H, dd, J=9, 7 Hz, H-4), 6.95 (1H, dd, J=9, 1 Hz, H-3), and 7.0-7.4 (5H, m, Ph).

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