A NEW ENTRY TO [2.3.4]CYCLAZINES

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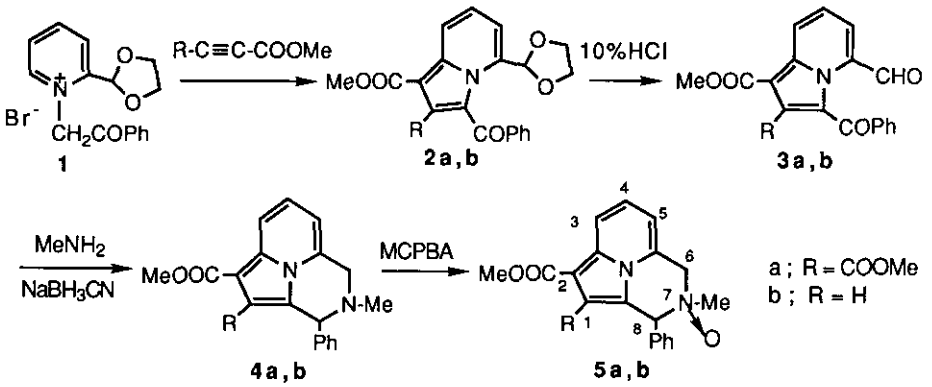
Abstract —— Treatment of 2,3-dihydro-2-methyl-3-phenyl-1*H*-pyrazino[3,4,5-*cd*]indolizine 2-oxides (**5**) with trifluoroacetic anhydride gave new heterocyclic six-membered betaines (**6**) which underwent 1,3-dipolar cycloaddition reaction with dimethyl acetylenedicarboxylate and maleimides in hot 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*-3a-aza-3-azulenylmethylene)succinate[2] 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)pyridine[5] 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 (**3**)(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 (**5**)(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

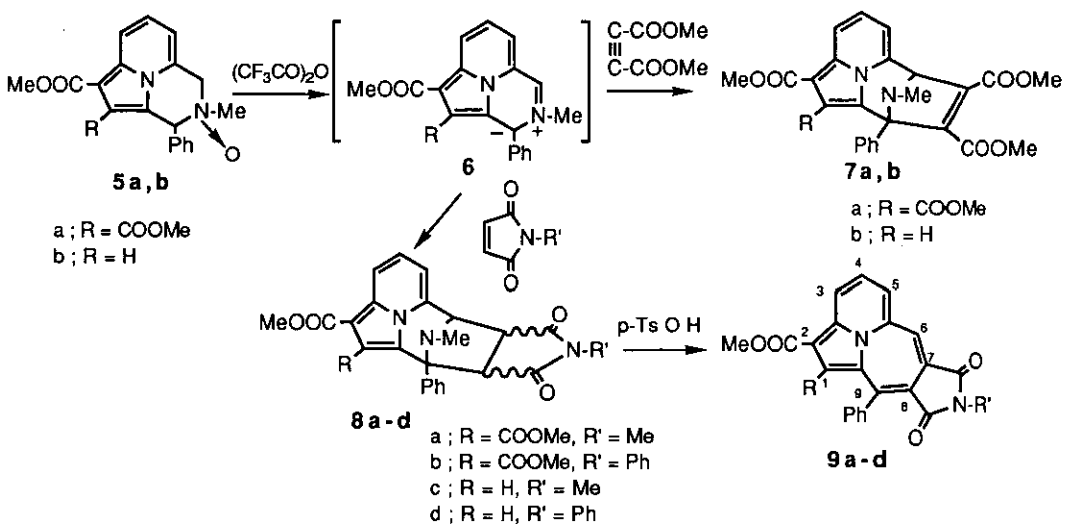


Table 1. 1,3-Dipolar cycloaddition of **6** with maleimides

8	R	R'	Yield(%)	(*exo*:*endo*)
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

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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 (ν, cm^{-1}, nujol) 1675, 1710, 1740, and 1785; ^{1}H-nmr (δ, ppm, 200 MHz, $CDCl_3$) 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 (ν, cm^{-1}, nujol) 1685, 1735 and 1780; ^{1}H-nmr (δ, ppm, 200 MHz, $CDCl_3$) 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 (ν, cm^{-1}, $CHCl_3$) 1670, 1700, and 1745; ^{1}H-nmr (δ, ppm, 200 MHz, $CDCl_3$) 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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