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A Facile Synthesis of 2-Substituted γ-Pyrone

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The substituted γ-pyrone unit is present as structural features of several natural products such as LL-Z1220,[1] tridachione,[2] ilikonapyrone,[3] peroniatriol I, and II.[4] Although a variety of synthetic methods have been developed for the construction of the pyrone ring, often they required multistep sequence and/or strong acidic conditions.[5]

We now wish to describe a simple one-pot synthesis of γ-pyrones from enol silyl ethers and diazomalonaldehyde in the presence of metal catalyst.

$$ \text{(1)} $$
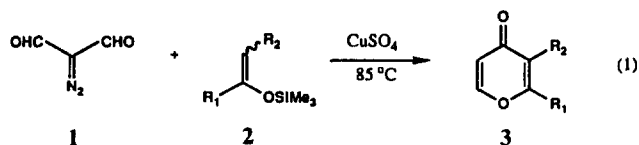
The reaction of diazomalonaldehyde (1)[6] with 1-phenyl-1-(trimethylsilyloxy)ethene, 2-(trimethylsilyloxy)propene, 4-(trimethylsilyloxy)-3-penten-2-one at 85℃, catalyzed by CuSO₄, gave pyrones 3a, 3b, and 3c in 58, 55, and 82% yields, respectively (Eq. (1)). But the same type of reaction between the diazo compound and 1-(trimethylsilyloxy)cyclohexene, 1-(trimethylsilyloxy)-1,3-butadiene, 2-(trimethylsilyloxy)furan, 3-(trimethylsilyloxy)-3-buten-2-one, butyl trimethylsilyl ketene acetal did not succeed. Other catalysts, including Pd(OAc)₂, Rh₂(OAc)₄, Cu(OAc)₂ were also investigated in the pyrone-forming reaction, but they were found to be either not active or less efficient than CuSO₄. The reaction seems to proceed via [4+2] cycloaddition of formylketen[5h,7] which was formed from 1 with enol silyl ether, followed by elimination of trimethylsilanol to give γ-pyrones 3[8] (Scheme 1). The results are summarized in the Table 1.

A representative procedure follows. To the suspension of
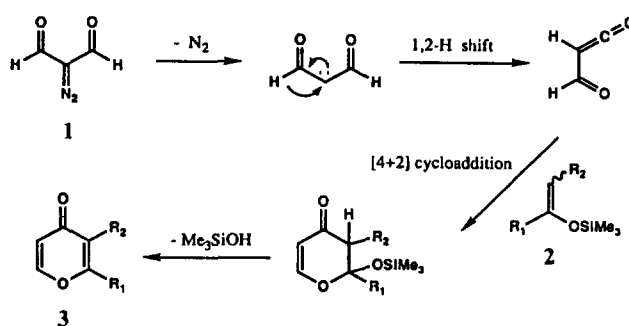
Scheme 1.

Table 1. Reaction of Diazomalonaldehyde 1 with Enol Silyl Ethers[a]

Entry	Reactant	Catalyst	Product	R₁	R₂	Yield (%)[b]
1	2a	None	3a	Ph	H	No reaction
2	2a	CuSO₄	3a	Ph	H	58
3	2a	Rh₂(OAc)₄	3a	Ph	H	29
4	2a	Cu(OAc)₂	3a	Ph	H	No reaction
5	2a	Pd(OAc)₂	3a	Ph	H	No reaction
6	2b	CuSO₄	3b	Me	H	55
7	2b	Rh₂(OAc)₄	3b	Me	H	36
8	2c	CuSO₄	3c	Me	COMe	82

[a] All reactions were carried out in benzene at 85℃ under Ar.
[b] Isolated yield.

anhydrous CuSO₄ (10 mg, 0.06 mmol) and 1-phenyl-1-(trimethylsilyloxy)ethene (2a, 570 mg, 3 mmol) in benzene (1 ml) at 85℃ was added a solution of diazomalonaldehyde (98 mg, 1 mmol) in benzene (5 ml) over 10 h, and then the mixture was stirred at 85℃ for another 6 h under argon atmosphere. The excess solvent and 2a were removed under vacuum, and the residue was purified by chromatography (silica gel, 1 : 4 EtOAc/hexanes) to provide 100 mg (58%) of 3a as a white solid; mp. 101-102℃ (recrystalized from hexanes) [lit.[5d] 101-103℃]; IR (KBr)=C-H 3079 (m), C=O 1696 (s), C=C 1625 (s) cm⁻¹; ¹H-NMR (CDCl₃) δ 7.8 (d, 1H, J=5.9 Hz, H-6), 7.7-7.4 (m, 5H, phenyl-H), 6.7 (d, 1H,

$J=2.4$ Hz, H-3), 6.3 (dd, 1H, $J=5.9$ and 2.4 Hz, H-5); ^{13}C-NMR (75 MHz, CDCl$_3$) 179.2 (C-4), 163.9 (C-2), 154.8 (C-6), 117.1 (C-5), 112.3 (C-3), 131.1 (C'-1), 125.7 (C'-2), 129.4 (C'-3), 131.4 (C'-4); MS *m/e* (relative intensity) 172 (M$^+$, 98), 144(78), 115(36), 102(100), 77(38). Anal. Calcd for C$_{11}$H$_8$O$_2$: C, 76.73; H, 4.68. Found; C, 76.62; H, 4.89.

In conclusion, the copper sulfate-catalyzed reaction of diazomalonaldehyde with enol silyl ether provides a convenient method for construction of 2-substituted Y-pyrones.

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7. For photolytic conversion of 1 into formylketene, see: G. Maier, H. P. Reisennauer, and T. Sayrac, *Chem. Ber.,* **115**, 2192 (1982).
8. Trimethylsilanol was detected by GC-Mass from crude reaction mixture.

Photochemical Interaction between Harmaline and DNA

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A few β-carboline alkaloids have been known to be phototoxic to bacteria and yeast.[1-4] Several observations strengthen the view that DNA and probably other macromolecules can serve as targets for the phototoxicity of β-carbolines but its action mechanism is not fully understood.[5-8] In the course of studies on the elucidation of phototoxicity mechanism of β-carboline alkaloids, we[9,10] previously reported that these compounds photochemically produce singlet oxygen and superoxide anion radicals in the presence of oxygen, while produce carbolinyl radicals under anaerobic conditions. One of β-carboline derivatives, harmaline photochemically produces a cycloaddition product with fumaronitrile.[11]
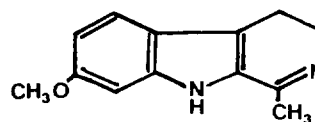
Harmaline

Scheme 1.

Photochemical reaction of harmaline with DNA was studied in order to make insight into the phototoxicity mechanism of β-carbolines. UV absorption spectrum of harmaline was not so strongly but somewhat affected by increasing DNA (Sigma, type I) concentration indicating weak ground state complexation between harmaline and DNA. UV absorption spectral changes of harmaline (1×10^{-4} M in H$_2$O) in the presence of calf thymus DNA (0.05 mg/cc) with time of irradiation show that the absorption maximum of harmaline at 375 nm gradually decreased and an isosbestic point was observed at 320 nm. Similar results were obtained when the reactions were run without DNA but far more slower rate. The relative absorbance decrease at 375 nm was in the order of the reaction runed with DNA under N$_2$> with DNA under O$_2$> without DNA under N$_2$ or O$_2$. The absorbance at 375 nm of harmaline in the presence of DNA under N$_2$ decreased more effectively than under O$_2$ strongly suggesting that the double bond of harmaline disappeared *via* photochemical reaction with DNA and this photoreaction is likely to proceed through its triplet excited state.

The photochemical modification in the helical structure of DNA in the presence of harmaline was investigated by monitoring the changes in circular dichroism spectrum. A 0.01 M NaCl solution of harmaline (1×10^{-4} M) and calf thymus DNA ($A=1.0$ at 260 nm) was irradiated with 350 nm UV light under N$_2$. The CD spectral changes with time of irradiation are shown in Figure 1. Both positive and negative band of the CD spectrum decreased significantly on irradiation. It has been known that when DNA is irradiated in the presence of the bifunctional psoralen, 8-MOP, both the negative and positive bands in the CD spectrum were affected to a similar extent.[12] However, in the presence of monofunctional 1,4-diphenylbutadiyne[13] or 5,7-dimethoxycoumarin, the negative band of the CD spectrum remained unperturbed but positive band increased with time of irradiation. The results suggest that the photochemical interaction of harmaline and DNA involves cross-linking of DNA double strands.

Photo-crosslinking of DNA by harmaline is further demonstrated by melting temperature profiles. As shown on Figure 2, the irradiation of DNA in the presence of harmaline under