

PHOTOADDITION OF β -DICARBONYL COMPOUNDS TO NITROGEN HETEROCYCLES (1)

James W. Pavlik* and Mohammad S. Farahat
Department of Chemistry, Worcester Polytechnic Institute,
Worcester, MA 01609, USA

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ABSTRACT. 2,4-Pentanedione and methyl acetoacetate undergo photoaddition to 1-methylpyrrole. The initial 1:1 adducts undergo a secondary photoelimination reaction to yield 3-acetyl-1-methylpyrrole. Methyl acetoacetate also undergoes photoaddition to 1-methylimidazole and 1,2-dimethylimidazole to yield photostable 1:1 adducts. These photoadditions are suggested to proceed *via* unstable oxetane intermediates that undergo spontaneous ring opening.

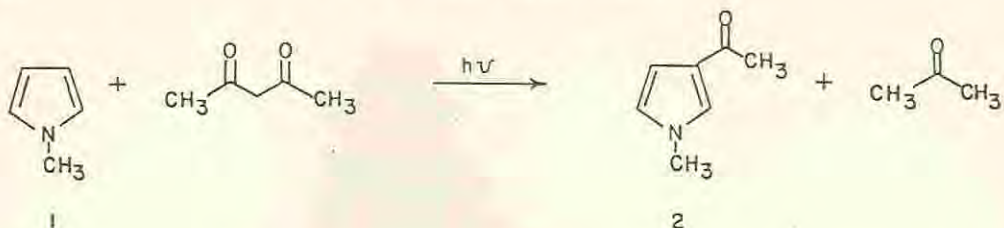
INTRODUCTION

Paterno-Büchi type photocycloaddition reactions of monocarbonyl compounds to heterocyclic systems usually produce oxetanes which may undergo subsequent ground-state rearrangements to more stable compounds (2). Furans form stable oxetanes with a variety of carbonyl compounds (3,4). Sulfur heterocycles, however, may require simple ring substitution while nitrogen heterocycles require electron withdrawing substituents on nitrogen for stable oxetane formation (5-8). When oxetanes are not isolated due to their instability, hydroxyalkyl or hydroxyaryl substituted heterocycles are usually formed. Photoaddition of aliphatic aldehydes and ketones to pyrroles, for example, takes place regiospecifically to give 3-substituted pyrroles. The intermediacy of oxetanes in these reactions has been suggested based on NMR evidence (9).

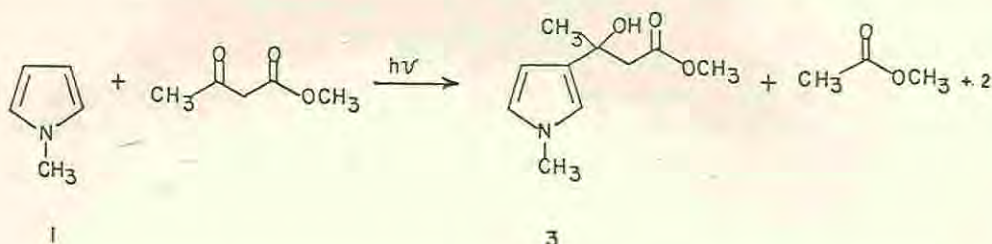
Although the photocycloaddition reactions of a variety of simple aldehydes and ketones to nitrogen heterocycles have been studied, much less is known about the photoaddition of dicarbonyl compounds. We wish to report that β -diketones and β -ketoesters also undergo photoaddition to these heterocycles. In some cases the initial 1:1 adduct undergoes a secondary photoelimination process to yield a 3-acylheterocycle.

RESULTS AND DISCUSSION

Irradiation of 2,4-pentanedione or methyl acetoacetate in the presence of 1-methylpyrrole 1 led to the formation of the same photoproduct. Mass spectral analysis of this product ($M^+ = 123$) indicated that it was a 1:1 condensation product with loss of C_3H_6O or $C_3H_6O_2$ respectively. GC and GC-MS analysis of the product mixtures revealed that loss of these molecular units was due to the formation of acetone or methyl acetate. This information, along with the infrared spectrum (1650 cm^{-1} ; conjugated carbonyl) 1H NMR (δ 2.1, s, 3H; 3.5, s, 3H; 5.8, m, 1H; 6.4, m, 2H) indicated that the product was an acetyl-1-methylpyrrole. Direct chromatographic and spectroscopic comparison of the isolated product with authentic samples of 2- and 3-acetyl-1-methylpyrrole (9, 10), confirmed that the product is 3-acetyl-1-methylpyrrole 2.

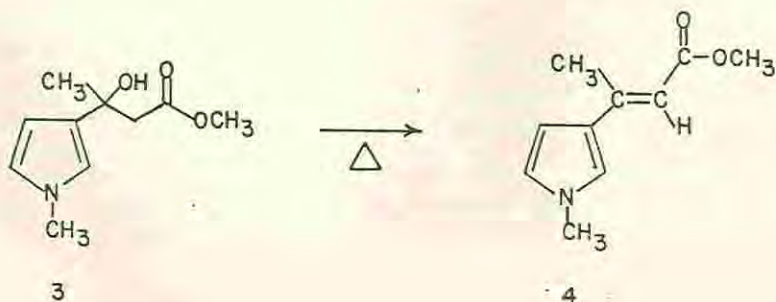


Although this was the only product detected from photoreaction of 2,4-pentanedione with 1-methylpyrrole, distillation allowed isolation of an additional product in 45% yield from the reaction with methyl acetoacetate. This product exhibited a parent peak in the mass spectrum at m/z 197 indicative of a 1:1 addition product. The infrared and ^1H NMR spectra were consistent with the assigned structure 3, methyl 3-hydroxy-3-(1-methylpyrrol-3-yl)butanoate. The methyl 3-hydroxybutanoate side chain was confirmed by the infrared spectrum which exhibited



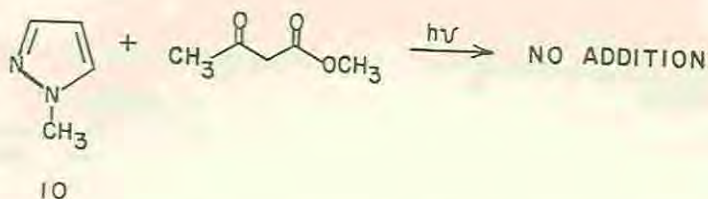
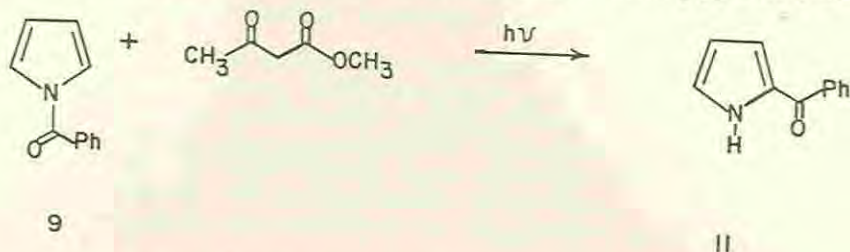
an ester carbonyl absorption at 1725 cm^{-1} and a broad hydroxyl absorption at 3500 cm^{-1} and by the ^1H NMR spectrum which shows 3H singlets at δ 1.5 and 3.6 (C-CH₃ and O-CH₃), a broad deuterium exchangeable signal at δ 3.9, and an AB quartet for the non-equivalent protons in the methylene group. The location of this side chain at position 3 of the pyrrole ring was confirmed by the ^1H NMR spectrum that showed ring multiplets at δ 5.9 (1H) and 6.4 (2H) due to the ring protons at C-4 and at C-2 and C-5 respectively (11).

Product 3 was particularly susceptible to dehydration and was partially converted to the α,β -unsaturated ester 4 upon vacuum distillation or during gas chromatographic analysis of 3, or more completely by heating 3 at 205° at atmospheric pressure. Flash chromatography on silica gel allowed isolation of 4 as a white crystalline solid. The changes in the spectral properties were



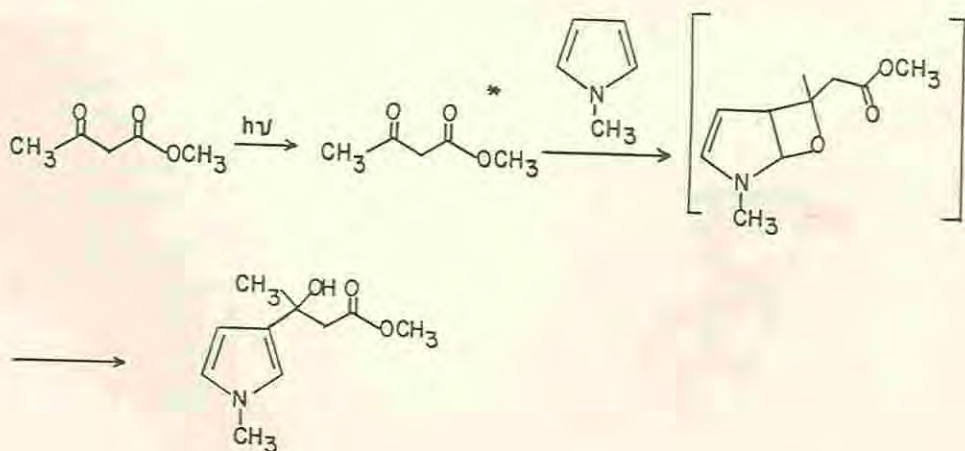
and 8 in yields of 3% and 8% respectively. Interestingly, adducts 7 and 8 showed no tendency to undergo photoelimination analogous to the reaction of 3 \rightarrow 2. Even after prolonged irradiation of 7 or 8 no conversion of these adducts or formation of products could be detected.

Methyl acetoacetate did not undergo photoaddition to 1-benzoylpyrrole 9 or to 1-methylpyrrole 10. In the former case, however, 1-benzoylpyrrole 9 was



observed to undergo isomerization to 2-benzoylpyrrole 11 upon irradiation in the presence of methyl acetoacetate. The yield of photoisomerization of 9 to 11 decreased upon irradiation in the absence of methyl acetoacetate. This suggests that the photoisomerization process is sensitized by methyl acetoacetate. The photoisomerization of 1-acetylpyrrole to 2- and 3-acetylpyrrole has been reported (13) and it is expected that both isomerizations follow the same mechanism.

The photoaddition reactions of methyl acetoacetate are suggested to occur via unstable (2+2) oxetane adducts. Although the suggested oxetane intermediates



could not be detected by spectroscopic examination of the crude product mixtures, the rearrangement of the amino ether linkage would be expected to be rapid. Since such photoadditions would be expected to occur in a head-to-head manner (3), the suggested mechanism is also consistent with the observed regioselectivity that leads to substitution only at the 3-position. Finally, methyl acetoacetate has been reported to yield stable oxetanes upon photolysis in cyclohexene (14). In this case, however, several additional cross-coupled products were formed from a radical pathway initiated by intermolecular hydrogen abstraction. For the reactions studied here, no cross-coupled products could be detected indicating that only Paterno-Büchi type photoaddition operates in these cases.

The lack of photoaddition of methyl acetoacetate to 1-benzoylpyrrole and 1-methylpyrazole may be due to the deactivation of the excited β -ketoester by the ground states of these heterocycles by an energy transfer process (15). Indeed, methyl acetoacetate appears to sensitize the phototransposition of 1-benzoylpyrrole.

The much lower reactivity of 2,4-pentanedione toward photoaddition (yield $\sim 1\%$) is attributed to the high concentration of the enol form. Because of this tautomerization, photoaddition of 2,4-pentanedione to alkenes usually proceeds by the addition of the enol double bond to the alkene rather than via addition of the carbonyl group (16). The increased reactivity of the non-enolizable 3,3-dimethyl-2,4-pentanedione is consistent with this suggestion.

EXPERIMENTAL

General. NMR spectra were recorded at 60 MHz on a Hitachi Perkin-Elmer (PE) R-24B spectrometer. Chemical shifts were measured relative to internal $(\text{CH}_3)_4\text{Si}$. IR spectra were recorded on a PE-683 spectrophotometer interfaced to a PE-3600 Data Station. GC was performed on a PE-3920 FID instrument equipped with either a 2 ft, 6 ft, or 10 ft \times 1/8 in column packed with 2% carbowax 20M-TPA on chromosorb G. GC-MS spectral analysis were performed on a Hewlett-Packard 5890 gas chromatograph equipped with an HP 5970 mass selective detector. Elemental analyses were determined by MicAnal, Tucson, AZ.

Reactants. Methyl acetoacetate, 1-methylpyrrole, 1-methylimidazole, 1,2-dimethylimidazole, and 2,4-pentanedione are commercially available and were either distilled or recrystallized before use. 3,3-Dimethyl-2,4-pentanedione (17), 2-acetyl-1,3-dioxolane (18), 1- and 2-benzoylpyrrole (19), and 1-methylpyrazole (20) were prepared according to literature procedures.

Irradiations. All irradiations were carried out using a 450 W Hanovia high pressure mercury lamp which was housed in a quartz immersion well and was cooled by flowing tap water. A corex sleeve was used around the lamp for all reactions except for reactions of 5, 6, and 10. In these cases a pyrex sleeve was used. Preparative reactions were carried out on a 325 ml scale under continuous flow of nitrogen. Concentrations in the range of 0.25–2.0 M in acetonitrile solvent were used.

Photoaddition of 2,4-Pentanedione to 1-Methylpyrrole (I). A solution (325 ml) of acetonitrile containing 32.5 g (0.325 mole) 2,4-pentanedione and 26.4 g (0.325 mole) 1-methylpyrrole was irradiated for 68 hrs. The resulting yellow solution was concentrated by rotary evaporation and the dark orange residue was distilled. Starting materials were collected from 80–101°C at atmospheric pressure. The dark brown residue was further distilled at reduced pressure to yield 3-acetyl-1-methylpyrrole 2, bp 110° (3.5 torr); 0.150 g (1.2 mmol, 0.4 % uncorrected yield); IR ν_{max} cm^{-1} (neat): 1650, 1350; ^1H NMR (CDCl_3) δ 2.35 (s, 3H), 3.65 (s, 3H) 6.40 (m, 2H), 7.14 (m, 1H); MS, m/z (rel. int.) 123 (47), 108 (100), 80 (15), 53 (29), 39 (34), 28 (32).

Photoaddition of Methyl Acetoacetate to 1-Methylpyrrole (1). A solution of acetonitrile containing 9.5 g (0.081 mole) methyl acetoacetate and 26.4 g (0.325 mole) 1-methylpyrrole was irradiated for 43 hours. The resulting pale yellow solution was concentrated by rotary evaporation and the yellow residue was distilled. Starting materials were collected up to 100°C at atmospheric pressure. The residue was further distilled at reduced pressure to yield 8.0 g of a colorless oil (boiling range 100–115°C at 1.0 torr). 2.0 g of this oil was flash chromatographed on a 30 mm diameter glass column packed with 20 cm silica gel. The column was eluted with hexane-ethyl acetate (9:1) and 49 fractions were collected (1–5, 50 ml; 6–31, 35 ml; 32–49, 30 ml). Fractions 14–26 were concentrated to yield methyl 3-(1-methylpyrrol-3-yl)but-2-enoate 4 as white crystals, mp 56–57°C; IR ν_{\max} cm^{-1} (KBr): 1690, 1615; $^1\text{H NMR}$ (CDCl_3) δ 2.73 (s, 3H), 3.51 (s, 3H), 3.62 (s, 3H), 5.92 (s, 1H), 6.22 (m, 1H), 6.41 (m, 1H) and 6.68 (m, 1H); MS, m/z (rel. int.) 179 (73), 148 (100), 147 (76), 121 (25), 120 (30), 119 (33), 118 (42), 108 (12), 106 (14), 105 (16), 104 (16), 91 (18), 81 (39), 77 (36), 63 (19). Anal. Calcd. for $\text{C}_{10}\text{H}_{13}\text{NO}_2$: C, 67.04; H, 7.26; N, 7.82. Found: C, 66.76; H, 7.29; N, 7.82. Fractions 37–45 were concentrated to yield methyl 3-hydroxy-3-(1-methylpyrrol-3-yl)butanoate 3, 0.850 g; IR ν_{\max} cm^{-1} (neat): 3500, 1725; $^1\text{H NMR}$ (CDCl_3) δ 1.48 (s, 3H), 2.6, 2.8 (AB quartet, 2H), 3.45 (s, 3H) 3.55 (s, 3H), 5.90 (m, 1H) and 6.37 (m, 2H); MS, m/z (rel. int.) 197 (16), 180 (16), 179 (100), 149 (15), 148 (99), 147 (59), 124 (78), 121 (47), 120 (40), 119 (39), 118 (28), 108 (77), 106 (34), 105 (26), 104 (20), 82 (71), 81 (50), 77 (35).

Photoaddition of Methyl Acetoacetate to 1,2-Dimethylimidazole (6). A solution (325 ml) of acetonitrile containing 18.9 g (0.163 mole) methyl acetoacetate and 15.6 g (0.163 mole) of 1,2-dimethylimidazole was irradiated for 40 hours. The resulting solution was concentrated by rotary evaporation and the orange residue was distilled under reduced pressure (1.8 torr) to recover starting materials (boiling range 38–60°C). The dark brown residual tar was treated with ether to provide 1.4 g of yellow crystals. After sublimation at 15 torr, 0.5 g of the crude crystals gave methyl 3-(1,2-dimethylimidazol-3-yl)butanoate 8 as white crystals: mp 106–107°C; 0.30 g; IR ν_{\max} cm^{-1} (KBr): 3180, 1725; $^1\text{H NMR}$ (CDCl_3) δ 1.50 (s, 3H), 2.34 (s, 3H), 2.7, 3.0 (AB quartet, 2H), 3.46 (s, 3H), 3.59 (s, 3H), 6.52 (s, 2H); MS, m/z (rel. int.) 212 (6), 194 (8), 139 (100), 123 (29), 121 (15), 99 (16). Anal. Calcd for $\text{C}_{10}\text{H}_{16}\text{NO}_2$: C, 56.59; H, 7.60; N, 13.19. Found C, 56.40; H, 7.67; N, 13.15.

Photoaddition of Methyl Acetoacetate to 1-Methylimidazole (5). A solution (325 ml) of acetonitrile containing 18.9 g (0.163 mole) methyl acetoacetate and 13.4 g (0.163 mole) of 1-methylimidazole was irradiated for 73 hrs. The resulting solution was concentrated by rotary evaporation and the residue distilled at reduced pressure (2.0 torr) to recover starting materials (boiling range 28–42°C). The dark brown residual tar was repeatedly extracted with small portions of ether. Evaporation of the ether left a yellow oil. This oil (0.100 g) was subjected to purification by preparative tlc on two 25 x 25 cm glass plates coated with silica gel. After two developments in CHCl_3 , the region between 10 and 35 mm from the origin was scraped from the plates and washed with CH_2Cl_2 . Concentration of this extract gave methyl 3-hydroxy-3-(1-methylimidazol-4-yl)butanoate 7 as a colorless oil: IR ν_{\max} cm^{-1} (neat): 3400, 1725; $^1\text{H NMR}$ (CDCl_3) δ 1.47 (s, 3H), 2.7, 3.0 (AB quartet, 2H), 3.53 (s, 6H), 6.67 (m, 1H), 7.07 (m, 1H).

Photolysis of 3-Hydroxy-3-(1-Methylpyrrol-3-yl)butanoate (3). A solution (5 ml) of acetonitrile containing 0.5 g (2.5×10^{-3} mole) of the adduct was irradiated through corex for 72 hrs. Analysis of the resulting solution by GC showed 43% conversion of the reactant and quantitative formation of 3-acetyl-1-methylpyrrole 2 and methyl acetate.

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