The Photochemical [2 + 2] Cycloaddition to *N*-Methoxycarbonyl-5,6-dihydro-4-pyridone

Philippe Guerry and Reinhard Neier*

Institut für organische Chemie, Universität Fribourg, Pérolles, CH-1700 Fribourg, Switzerland

The *N*-methoxycarbonyl-5,6-dihydro-4-pyridone (**1**) undergoes photochemical [2 + 2] cycloaddition with a series of differently substituted alkenes in high yield and with extremely high regioselectivity.

Inter-[1] and intra-molecular[2] photochemical [2 + 2] cycloadditions have been used as key steps to prepare natural products of widely different structure.[3] Often mixtures of regio- and stereo-isomers are obtained;[2c,4] as is the case for most photochemical reactions, the influence of slight variations of the substrates or of the reaction conditions can change the results dramatically.[1b,1c] Therefore, the behaviour of each chromophore must be studied individually.

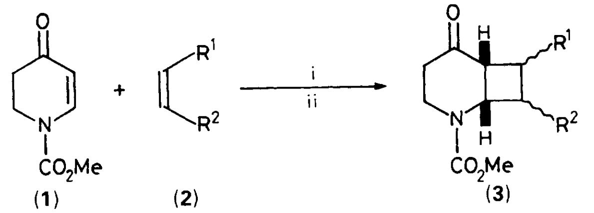
Recently the photochemical [2 + 2] cycloaddition of a series of *N*-alkyl-5,6-dihydro-4-pyridones has been reported.[5] On irradiation the 5,6-dihydro-4-pyridones reacted readily with electron-poor alkenes to provide bicyclic or tricyclic products in good yield. Mixtures of diastereo- and regio-isomers were obtained. The separation of these mixtures proved to be difficult, owing to the instability of the aminoketone formed. The fragmentation of the cyclobutane ring is facilitated to an unusual extent by the lone pair of the nitrogen. In order to improve the stability of the products, we decided to change the protecting group on nitrogen. With the methoxycarbonyl group as a substituent on nitrogen, the photochemical reaction transforms a vinylogous *N*-acylcarbamate into a ketocarbamate, which should be more stable.

Table 1. Photochemical [2 + 2] cycloaddition of the dihydropyridone (**1**) with alkenes.

Entry	Alkene	*T*/°C; irrad. *t*/h	Product	Yield/% (*exo*/*endo* ratio)
1	(**2a**)	−70; 1.50	(**3a**)	93
2	(**2b**)	room temp.; 1.5	(**3b**)	73 (6 : 4)
3	(**2c**)	room temp.; 2.0	(**3c**)	85[a]
4	(**2d**)	room temp.; 2.0	(**3d**)	96 (7 : 3)
5	(**2e**)	room temp.; 1.3	(**3e**)	80 (7 : 3)[b]
6	(**2f**)	room temp.; 1.5	(**3f**)	73 (8 : 2)[b]

[a] One of the diastereoisomers was obtained crystalline in 75% yield.
[b] The assignment of the *exo vs. endo* product was not unequivocally possible for the products (**3e**) and (**3f**).

The *N*-methoxycarbonyl-5,6-dihydro-4-pyridone (**1**) could be easily synthesized in three steps from the commercially available 4-nitropyridine *N*-oxide according to Raucher.[6] Compound (**1**) reacted readily, under irradiation, with a series of alkenes to give the [2 + 2] cycloadducts in excellent yields

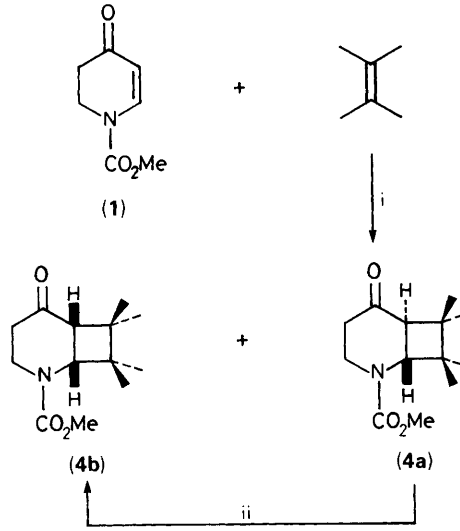


a; $R^1 = R^2 = H$
b; $R^1, R^2 = (CH_2)_3$
c; $R^1 = R^2 = CO_2Me$
d; $R^1 = H, R^2 = CO_2Me$
e; $R^1 = H; R^2 = O(CH_2)_3Me$
f; $R^1 = H; R^2 = CH_2Ph$

Scheme 1. *Reagents and conditions:* i, (**1**) (8 mmol) and (**2b—f**) (16 mmol) in acetone (125 ml) were irradiated with a 125 W medium pressure mercury lamp under nitrogen; ii, the crude product dissolved in ether (100 ml) was stirred with aluminium oxide (2.5 g) for 2 h at room temperature.

(Scheme 1, Table 1). As hoped, the isolation of the products was easier (chromatography at room temperature) and therefore higher yields (73–96%) could be obtained. The change of the protecting group on nitrogen furnished several unexpected advantages. The irradiation times became considerably shorter and the quantum yield for these cycloadditions is nearly optimal (Φ = 0.5—0.9).[7] Not only electron-poor alkenes but all tested alkenes, independent of the substituent, undergo cycloaddition reactions. Even more interesting were the results of the study of the regio- and stereo-selectivity of the cycloaddition. Using the alkene tetramethylethylene we obtained two diastereoisomers (**4a** and **4b**) in 85% yield in the ratio 6:4 (Scheme 2). The diastereoisomers could be separated by flash chromatography. The compound with the smaller R_f value, present in larger quantities, could be totally transformed into the other diastereoisomer by stirring an ether solution with aluminium oxide. This result is indicative of the presence of two diastereoisomers with a *cis*- and a *trans*-ring junction, respectively, which can be isomerized into the thermodynamically more stable *cis*-isomer.[4,8] The coupling constants between the bridgehead hydrogens were similar to the values reported by Swenton[9] for the cycloadducts between 1,3-dimethyluracil and diethoxyethylene (J_{trans} 13.0, J_{cis} 10.0 Hz). Independent proof of the presence of the two diastereoisomers was obtained from studies of the nuclear Overhauser enhancements (NOEs) between the four methyl groups and the bridgehead protons.

For the synthetic experiments the irradiation was followed directly by an equilibration with aluminium oxide. Using this two-step procedure, the number of isomers obtained could be reduced; mixtures of only two diastereoisomers (ratio 7:3) were obtained using methyl acrylate (**2d**) and n-butoxyethylene (**2e**) (Table 1). ^{1}H NMR studies proved that the cycloaddition for both alkenes had been completely regioselective. Furthermore, in contrast to the cycloadditions with cyclohexenones, the same regioisomer was obtained, independent of the character of the alkene substituent. The selectivity must be excellent because the total yields are very high (96 and 80%). As the ring junction can be equilibrated, the only relative configuration which cannot be controlled is the *endo*/*exo* selectivity for the substituent. The photochemical cycloaddition to (**1**) allows annelated cyclobutanes to be obtained with complete control of the regiochemistry. The two diastereoisomers can be easily separated by flash chromatography so that high yields of the cycloadducts are available. The only limitation of the photochemical cycloaddition is due to the fact that the 5,6-dihydro-4-pyridone (**1**) dimerizes also.



Scheme 2. *Reagents and conditions:* i, (**1**) (8 mmol) and tetramethylethylene (40 mmol) in acetone (125 ml) were irradiated with a 125 W medium pressure mercury lamp under nitrogen for 2 h; ii, (**4a**) (1 mmol) in ether (25 ml) was stirred with aluminium oxide (500 mg) for 2 h at room temperature.

If the concentration of the chromophore is kept sufficiently low (below 0.06 M) and an excess of the alkene is used (2—5 times), dimerization is not a problem. Kinetic studies showed that the quantum yield of the dimerization is considerably smaller than the quantum yields of the cycloaddition reaction.[7]

In conclusion, the *N*-methoxycarbonyl-5,6-dihydro-4-pyridone (**1**) is a reliable chromophore for photochemical [2 + 2] cycloadditions, which allows isolation of the regioselectively formed cyclobutane derivatives in high chemical yields.

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