

Photophthalimidation of Unactivated Double Bonds. Synthesis of Protected Phenethylamines

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Abstract

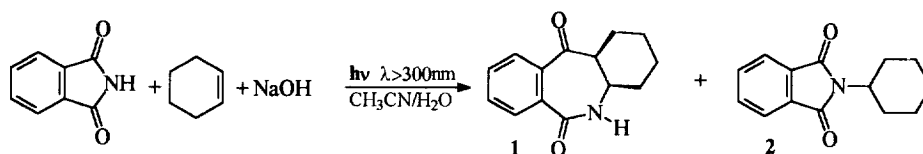
At low hydroxide ion concentrations, the photoaddition of phthalimide to cyclohexene, indene or styrene derivatives takes place. The cation radical obtained in the electron transfer from the alkene to excited phthalimide is trapped by phthalimide anion. At high hydroxide ion concentrations concerted [2+2] cycloaddition occurs that yields benzazepinediones, whatever the ionization potential of the alkene. The most suitable reaction conditions can be inferred from the observed fluorescence of phthalimide anion. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Photochemistry; Amination; Cycloaddition; Fluorescence.

The photochemistry of phthalimides in the presence of alkenes is known to involve the lowest singlet or triplet excited state [1-3]. T_1 photocycloaddition to the aromatic ring has been found to give *ortho* and *para* adducts [4-6]. S_1 takes part in two competitive processes, namely: concerted [2+2] cycloaddition to give benzazepinediones and single-electron transfer (SET) with alkenes with low ionization potentials. This latter process quenches the excitation (back electron transfer); in the presence of nucleophiles, however, the cation radical can be trapped and lead to addition products [7]. As shown in this paper, the photochemistry of the phthalimide/alkene/hydroxide ion system is strongly dependent on the HO^- concentration. Thus at $[HO^-] > [phthalimide]$, concerted photocycloaddition of the phthalimide ion singlet excited state is observed. On the other hand, at $[HO^-] < [phthalimide]$, a dramatic change in the reaction takes place by which photoaddition of phthalimide to the double bond of the alkene (*i.e.* photophthalimidation) occurs with styrene derivatives, such a process affords direct, ready access to protected phenethylamines. These compounds are important as such and as intermediates in the preparation of many pharmaceuticals and in the synthesis of a structural variety of alkaloids [8].

A few years back, the authors found that irradiation of a *tert*-butanol solution of sodium phthalimide in a ten-fold excess of cyclohexene gave the expected benzazepinedione (**1**) in 35 % yield, together with solvent photoaddition products [9]. The solvent was excluded from the

reaction by using an acetonitrile:water mixture, also, in order to optimise the [2+2] photoadduct yield, the effect of the hydroxide ion concentration on the photochemistry of the phthalimide/cyclohexene system was studied.



A homogeneous solution of phthalimide, NaOH and cyclohexene in a 2:1:22 mole proportion was irradiated to obtain two main products, *viz.* the expected adduct **1** and *N*-cyclohexylphthalimide (**2**), in a 1.6:1 ratio (table 1, entry 1). While phthalimide (PHT-H) did not fluoresce, phthalimide anion (PHT⁻) fluoresced strongly ($\lambda_{\text{exc}} = 300\text{nm}$, $\lambda_{\text{em}} = 400\text{nm}$), the maximum emission intensity being reached at a phthalimide/NaOH ratio of 2:3. Addition of cyclohexene was found to quench the fluorescence, thus confirming the involvement of the singlet excited state of the imidate in the photocycloaddition. At a higher NaOH concentrations, irradiation under conditions of maximally quenched fluorescence (table 1, entry 2), increased the yield of 1,5-benzazepinedione (**1**) but decreased that of **2**. On the other hand, at NaOH concentrations below 1/10 that of phthalimide, photocycloaddition was almost suppressed and photophthalimidation was the dominant process (table 1, entry 3). Under these conditions, no fluorescence of phthalimide anion was detected, so its involvement as the electronically excited species was excluded. Consequently, the formation of **1** under these conditions is likely due to γ -hydrogen abstraction from excited **2** [10].

Table 1.

Effects of the NaOH concentration on the photoreaction of Phthalimide with Cyclohexene.

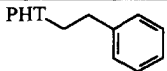
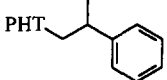
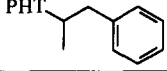
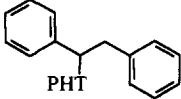
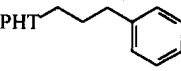
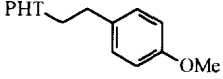
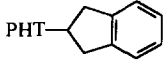
Entry	PHT-H equiv	NaOH equiv	Cyclohexene equiv	Conversion (%)	Isolated yield (%)	
					1	2
1	6.8	3.4	75	80	40	25
2	6.8	10.2	75	88	84	< 5
3	6.8	0.5	75	44	< 10	70

Under the conditions that minimised photocycloaddition, photophthalimidation of styrene derivatives as a direct, simple entry to β -phenylethylamines, was accomplished. Irradiation of the olefins with excess phthalimide in the presence of a small amount of alkali (Table 2, entries 1 to 6) afforded good yields of the addition products. The high concentration of PHT-H used prevents absorption of light by the olefins and also side reactions of the photophthalimidation products.

Table 2. Photophthalimidation of unactivated double bonds.^a

$$\text{PHT-H} + \text{C}=\text{C} + \text{NaOH} \xrightarrow[\text{CH}_3\text{CN}/\text{H}_2\text{O}]{h\nu} \text{PHT-C-C-H}$$

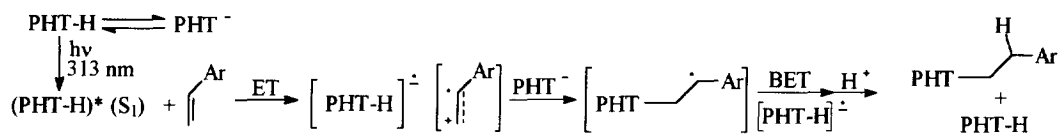
6.8 equiv 2.1 equiv 0.5 equiv

Entry	Olefin	Time (h)	Conversion (%)	Product	Yield ^b (%)
1	Styrene	8	75		53
2	α -Methylstyrene	4	80		90
3	β -Methylstyrene	12	60		44
4	<i>trans</i> -Stilbene	25	76		71
5	Allylbenzene	2	50		30
6	4-Methoxystyrene	4	90		70
7	Indene	6	75		90

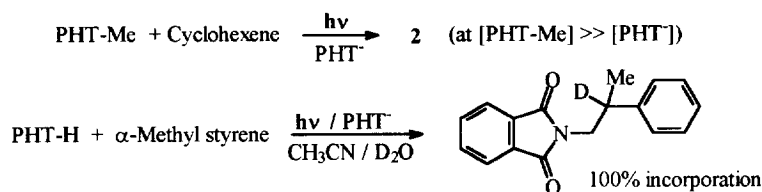
a) Irradiations were performed by using a 125 W medium-pressure mercury lamp in a Pyrex immersion well reactor. In a typical run, PHT-H, NaOH and olefin were dissolved in 150 ml of CH₃CN:H₂O (8:1) and irradiated for the stated time. Most of the CH₃CN was removed under vacuum, 100 ml of CH₂Cl₂ added and the organic layer washed with 5% aqueous NaOH solution to remove unreacted PHT-H. From the concentrated organic layer, the photoproducts were crystallised.

b) Yields are based on consumed olefin.

Mechanistically, light must be absorbed by phthalimide, which acts as a sensitizer. Electron transfer (ET) from the olefin to the phthalimide singlet excited state produces the radical-ion pair. The cation radical is trapped by phthalimide anion to give the most stable radical. Back electron transfer (BET), followed by protonation, yields the photoaddition product. This mechanism is consistent with the fact that no fluorescence from phthalimide anion was detected at the phthalimide/hydroxide ion ratio used, which confirms that light is absorbed by phthalimide.



The reaction was equally successful if phthalimide was replaced with *N*-methylphthalimide, which thus confirms its role as sensitizer. Anion protonation following back electron transfer in the last step was accomplished by quantitative incorporation of deuterium at the benzylic position when the reaction was conducted in deuterated water.



The use of intermolecular photoinduced nucleophilic addition of ammonia to styrene derivatives as a synthetic method for the preparation of phenethylamines was demonstrated elsewhere [11]. The reaction requires a sensitizer and the addition of arenes capable of stabilizing the cation radical produced. The work up procedure involves treatment with acetic anhydride-pyridine to protect the amine group, followed by chromatographic separation of the acetylated product, unreacted styrene, sensitizer and added arene. Photophthalimidation has the advantage that the sensitizer is also the nucleophile, the phenethylamines are already protected, and that the reaction is much easier to implement and the products more readily isolated.

Acknowledgements

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