Tetrahydrophthalic anhydride and imide: remarkably efficient partners in photochemical [2 + 2] cycloaddition reactions with alkenols and alkynols

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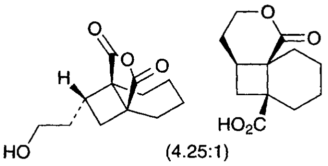
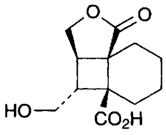
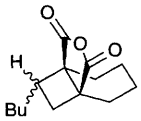
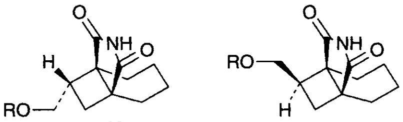
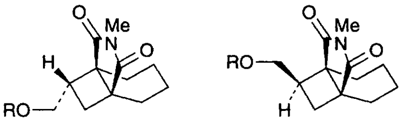
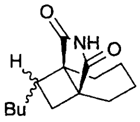
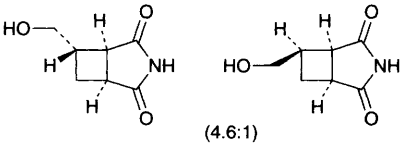
Intermolecular photochemical [2 + 2] cycloaddition of a variety of alken- and alkyn-3-ols with 3,4,5,6-tetrahydrophthalic anhydride (THPA) and the related imide 4 gave the corresponding cyclobutanes and cyclobutenes in high yield, after relatively short irradiation times, with stereoselectivities as high as 10:1 for the cyclobutane examples.

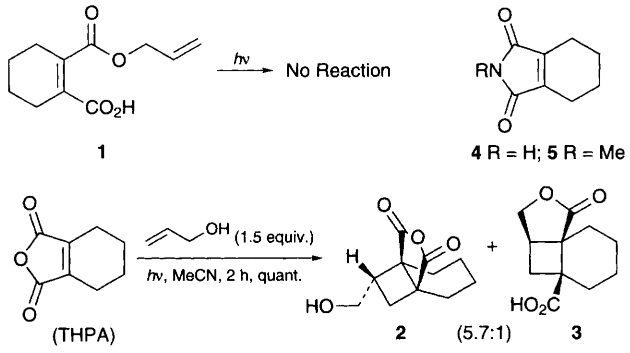
During part of a program involving the use of organic photochemistry in the total synthesis of cyclooctane containing natural products[1,2] we found that intramolecular [2 + 2] photocycloaddition of the acid-ester **1** failed under a variety of conditions, whereas intermolecular [2 + 2] photocycloaddition between 3,4,5,6-tetrahydrophthalic anhydride (THPA) and allyl alcohol proceeded smoothly to give a mixture of the hydroxy

Table 1 Photocycloaddition with alkenols

Entry	Reactants (1 : 1.5)	Yield (%)	Time	Products
a	THPA, but-3-ene-1-ol	88	4 h	 (4.25:1)
b	THPA, *cis* but-2-ene-1,4-diol	83	4 h	 **6**
c	THPA, hex-1-ene	90	5 h	 (2:1)
d	**4**, allyl alcohol	89	70 min	 **10** (R = H; 10:1)
e	**4**, allylethyl ether	92	75 min	(R = Et; 8.2:1)
f	**5**, allyl alcohol	77	4.5 h	 (R = H; 7:1)
g	**5**, allylethyl ether	80	5.5 h	(R = Et; 6.3:1)
h	**4**, hex-1-ene	42	5.5 h	
i	Maleimide, allyl alcohol	72	2 h	 (4.6:1)

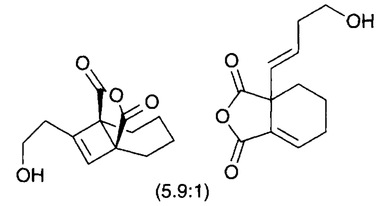
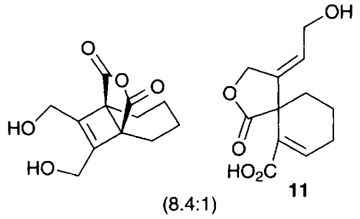
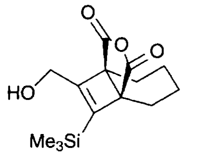
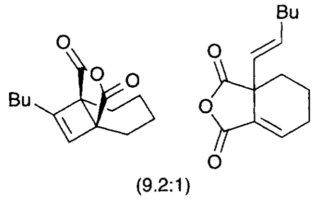
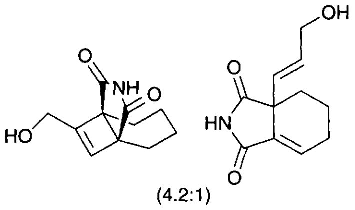
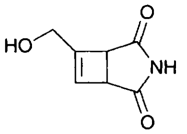
anhydride **2** and the acid-lactone **3** in essentially quantitative yield in a ratio of 5.7 : 1 (Scheme 1). This intermolecular photochemical [2 + 2] cycloaddition represents an extremely efficient synthetic process in that (*a*) only 1.5 equiv. of allyl alcohol is required, (*b*) a relatively low intensity 125 W medium-pressure mercury vapour lamp is used, (*c*) the reaction is complete within two hours and (*d*) an unusually high stereoselectivity is observed. The failure of **1** to undergo intramolecular cycloaddition and the fact that there is no formation (TLC) of **1** with THPA and allyl alcohol in MeCN under neutral conditions, before irradiation, confirms the intermolecular nature of the photocycloaddition.

Intrigued by these results we set out to explore the generality of the intermolecular [2 + 2] photocycloaddition of a variety of alkenols with THPA and the corresponding tetrahydrophthalimides **4** and **5**, the results of which are summarised in Table 1. In general the cycloadditions were both efficient and rapid giving the corresponding cyclobutanes in high yield, with excellent stereoselectivity, using 1.5 equiv. of the alkenols in all cases.† In most examples *exo*-addition, with respect to the alkenol substituent and the anhydride or imide moieties, was favoured resulting in the predominant formation of cyclobutane anhydrides and imides. With THPA the initially formed *endo*-adducts underwent spontaneous cyclisation to give lactone products. Particularly noteworthy in this respect is the reaction of THPA with *cis*-but-2-ene-1,4-diol (entry b) which gave the cyclobutane-lactone **6** as the sole product, in excellent yield, after only 4 h irradiation. The results of the cycloadditions of the



Scheme 1

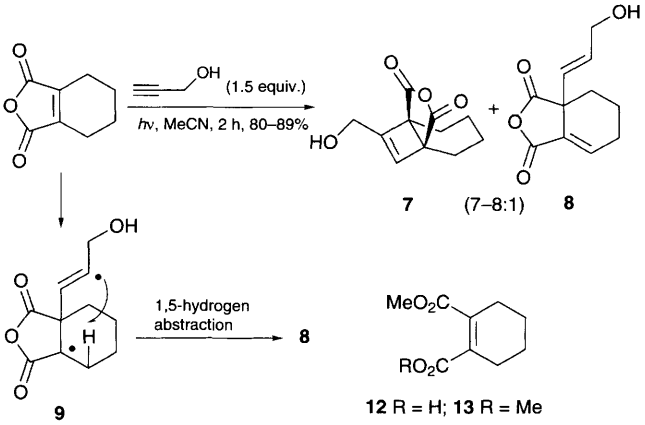
Table 2 Photocycloaddition with alkynols

Entry	Reactants (1 : 1.5)	Yield (%)	Time	Products
a	THPA, but-3-yne-1-ol	83	4 h	 (5.9:1)
b	THPA, but-2-yne-1,4-diol	75	6 h	 (8.4:1)
c	THPA, 1-trimethylsilyl-prop-1-yne-3-ol	68	3 h	
d	THPA, hex-1-yne	85	3 h	 (9.2:1)
e	**4**, prop-2-ynyl alcohol	72	2 h	 (4.2:1)
f	Maleimide, prop-2-ynyl alcohol	79	1 h	

imides **4** and **5** proved to be particularly interesting with respect to the nature of the alkenol derivative used. For example in entries d and e, allyl alcohol and the corresponding ethyl ether gave almost identical reaction times, yields and stereoselectivities. With the *N*-methyl derivative **5** longer reaction times were required but the yields and stereoselectivities were again very similar for both the free alcohol and ether (entries f and g). Excellent results were also obtained with simple alkenes such as hex-1-ene and THPA (entry c) although a realtively moderate 2 : 1 stereoselectivity was observed. With **4** and hex-1-ene a poorer yield (42%) was obtained (entry h) which was attributed to the fact that the reaction was slower and significant amounts of the photodimer of **4** was obtained due to a competing reaction. Photocycloaddition of allyl alcohol and maleic anhydride gave only unidentified polymeric material which we attributed to the instability of the resulting photoadduct although we were unable to prove this. Fortunately reaction of maleimide with allyl alcohol (entry i) proceeded well to give a good yield of the corresponding cycloadduct with reasonably high stereoselectivity.

We had also found that cycloaddition of THPA proceeded very efficiently with 1.5 equiv. of prop-2-ynyl alcohol to give the cyclobutene anhydride **7** in good yield[1,2] as well as a minor component which we initially did not characterise. On reinvestigation of this reaction on a larger scale we found that the minor component was actually the cyclohexene-anhydride **8** which we believe is formed from the initial triplet-biradical adduct **9** *via* a transannular 1,5-hydrogen abstraction[3] (Scheme 2). We believe that this is a competing minor reaction rather than a secondary photo product of **7**, as we found there was no formation of **8** on prolonged irradiation (24 h) of **7**. Furthermore there was no significant change in the product ratio on running the reactions with different stoichiometries of the starting materials.

Table 2 summarises the results of a number of photocycloadditions using a variety of alkynols. The cyclobutenes were formed rapidly and in good to excellent yields in all cases. With THPA and the imide **4** the 1,5-hydrogen abstraction products were formed, as minor products (10–15%), with all the alkynols investigated. The interesting spirocyclic lactone **11** formed by irradiation with but-2-yne-1,4-diol is a result of the initially formed abstraction product undergoing lactonisation. In the case of the 1-trimethylsilylprop-1-yn-3-ol (entry c) it appeared that a mixture of minor 1,5-abstraction products were formed (12%), but it was not possible to purify and characterise them. Not surprisingly maleimide (entry f) gave only the cyclobutene adduct as 1,5-hydrogen abstraction would be impossible. The efficiency of THPA and the corresponding imides as photopartners in [2 + 2] cycloadditions can be explained by the fact that the UV spectrum of THPA shows a λ_{max} = 301 nm (ε = 84), which coincides with the strong emission at 302 nm from the 125 W medium-pressure mercury vapour lamp used. Interestingly the THPA derivatives **12** and **13** failed to give any cycloaddition products with either allyl or prop-2-ynyl alcohol even after prolonged irradiation. These results, however, are easily explained by the fact that **13**, for example, shows λ_{max} = 220 nm (ε = 7,027) which is beyond the cut off point for the pyrex filtered UV source used in this study.



Scheme 2

In summary, tetrahydrophthalic anhydride and the corresponding imide have proved to be exceptionally efficient partners in intermolecular [2 + 2] photochemical cycloaddition reactions with alkenols and alkynols, giving high yields of cycloadducts with levels of stereoselection almost unprecedented in classical intermolecular cycloadditions.[4]

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Footnote

† Glassware consisted of a standard, water cooled Pyrex immersion well photochemical apparatus of 100 cm^3 reaction volume. All reactions were carried out in dry degassed CH_3CN (100 cm^3) with a concentration of 0.066 mol dm^{-3} of anhydride or imide. Irradiations were performed using a 125 W medium pressure mercury vapour lamp obtained from Osram HQL (MBF-U) bulbs. All new compounds were fully characterised by IR, ^{1}H and ^{13}C NMR, and either elemental analysis or HRMS. The relative stereochemistries of all the photoadducts were obtained by correlation of the ^{1}H NMR data to that of **2** and **10**, both of which were assigned individually by NOE experiments.

References

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