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Functionalisation of cycloalkanes: the photomediated reaction of cycloalkanes with alkynes

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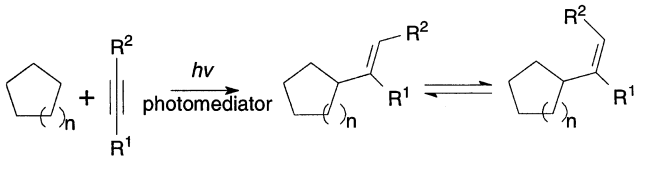
Abstract—Using a standard mercury vapour lamp or sunlight, and in the presence of a soluble or polymer-bound photomediator such as benzophenone, cycloalkanes can be functionalised by insertion of alkynes containing electron-withdrawing groups into a C–H bond. © 2001 Elsevier Science Ltd. All rights reserved.

The functionalisation of an unactivated alkane is a fundamental synthetic process of enormous practical importance.[1] It can be achieved using heme and non-heme based enzyme systems,[1] 'Gif chemistry'[2] and a number of other diverse methods.[3] In 1969 Buchi, and independently Grovenstein, noted that the irradiation of a cyclohexane solution of ethyl propiolate[4] or dimethyl acetylenedicarboxylate[5] gave very small amounts of products resulting from alkyne insertion into a C–H bond of the cycloalkane. In view of the reaction times and yields involved—24 h and 5%, and 10% and 14 days, respectively—it is not surprising that the system has not been revisited for over 30 years. We have now found that the use of a photomediator such as benzophenone has a dramatic effect on this system, reducing the reaction time to a few hours and, in the case of cyclopentane, giving yields as high as 70% (Scheme 1). The further observations that the reaction proceeds in sunlight and that an easily removed, and potentially recyclable, polymer-bound mediator can be used, support the conclusion that this photochemical functionalisation is a potentially important way of activating a saturated system.

The reaction is carried out by irradiating a cycloalkane solution of the alkyne (0.15 M) and the mediator (1 equiv.) through pyrex, using a medium pressure mercury lamp, until none of the alkyne remains (GC). Evaporation of the cycloalkane and removal of the mediator by chromatography gives a substituted alkene as the only low molecular weight product formed. The synthetic scope of the reaction has been explored in terms of both the alkyne and the cycloalkane component. In general, the reaction (Table 1) gives a mixture of *E*- and *Z*-alkenes as a result of a secondary photoisomerization process, the precise ratio being a function of the reaction time and mediator used. An electron-withdrawing group on the alkyne appears to be a prerequisite for reaction, as alkynes with electronically neutral (phenylacetylene, diphenylacetylene and 3-hexyne) and electron-donating groups (ethyl ethynyl ether) do not react. The reaction of monosubstituted alkynes results in regiospecific reaction at the unsubstituted alkyne carbon. The process is most efficient for cyclopentane, with C_6–C_8 cycloalkanes giving lower yields of approximately the same size. This effect may be an example of I strain,[6] a concept normally associated with reactions involving carbocation intermediates, but which has also been applied to radical reactions. Disubstituted alkynes are less reactive giving poorer yields with cyclopentane and cyclohexane, and failing to react with higher cycloalkanes.

The separation of the product from the mediator requires chromatography, thus making the process less attractive from the synthetic point of view. The polymer-bound mediator **1**[7] can however be used thus allowing pure product to be isolated by a simple filtration/evaporation sequence. The yield obtained is lower



R^1 = H, R^2 = EWG, n = 5 - 8: yield (*E* + *Z*) = 18 -70%
R^1 = R^2 = EWG, n = 5, 6: yield (*E* + *Z*) = 30 -50%

Scheme 1.

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Table 1. The photomediated[a] reaction of alkynes with cycloalkanes: representative examples

Cycloalkane	Alkyne	Time (h)	Yield (%)[b]	*E*:*Z*[c]
C5	Ethyl propiolate	2.5	70	1.33
C6	Ethyl propiolate	4.5	43	1.53
C7	Ethyl propiolate	2.5	40	1.00
C8	Ethyl propiolate	3.5	47	1.14
C5	DMAD	2.5	50	*Z* only
C6	DMAD[d]	20	15	0.29
C7	Isopropyl propiolate	2.75	36	1.25
C5	3-Butyn-2-one	11.5	18	3.90[e]
C5	Methyl propiolate	7.5	54	1.3[e,f]
C7	Methyl propiolate	32	26	1.4[g]
C5	Ethyl ethynyl ether	No reaction		
C5	Phenylacetylene	No reaction		
C5	Diphenylacetylene	No reaction		

[a] Rayonet reactor, pyrex vessel, 350 nm lamps, mediator: benzophenone, unless otherwise indicated.

[b] Isolated yield; all compounds were identified spectroscopically and all new compounds gave satisfactory elemental analyses.

[c] For isolated products, unless otherwise indicated.

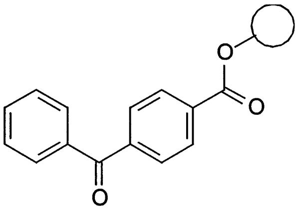
[d] Mediator: acetophenone.

[e] GC.

[f] Polymer-bound mediator.

[g] Light source: sunlight.

but the experimentally facile nature of the procedure makes the use of a polymer-bound mediator very attractive. Another interesting aspect of the system is the possibility of carrying out the reactions in sunlight. Although under these conditions the reactions were again slower and resulted in lower yields, the experimental set-up used for solar irradiation was not optimised and so the potential of this approach remains to be assessed. The formation of small amounts of two, as yet, unidentified by-products was also observed in this case.



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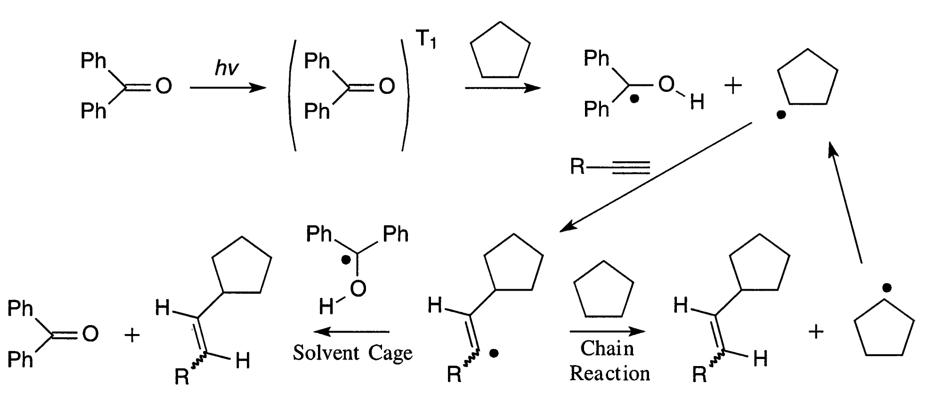
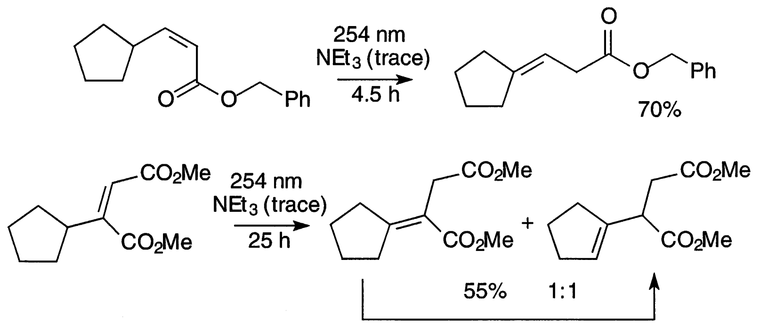
Mechanistically, the reaction can be viewed simply as an example of photosensitization. This would involve energy transfer from benzophenone, or its equivalent, to the alkyne which acting as a 1,2-biradical in its triplet state, could be involved in the key abstraction of hydrogen from the cycloalkane. The failure of either phenylacetylene ($E_T = 300$ kJ mol^{-1})[8] or diphenylacetylene ($E_T = 260$ kJ mol^{-1})[8] to react in the presence of benzophenone ($E_T = 287$ kJ mol^{-1})[8] suggests that this is not the case. Although reaction of the former is precluded on energy grounds, the sensitisation mechanism fails to account for the lack of reactivity of the latter. A mechanism (Scheme 2) in which the benzophenone abstracts a hydrogen atom from the cycloalkane[9] is thus preferred. In addition to providing a basis for the reaction in general, this mechanism also accounts for the significance of an electron-withdrawing group in the alkyne, as it would allow attack of the nucleophilic[10] cycloalkyl radical to be more competitive relative to hydrogen abstraction. In the absence of an electron-withdrawing group the latter process occurs exclusively, resulting in reversion to starting materials. In terms of how the vinyl radical proceeds to products, the data currently available do not distinguish between a cage effect promoted hydrogen abstraction from the benzhydryl radical, and hydrogen abstraction from a cycloalkane molecule which would occur as part of a chain mechanism.

The range of materials available from this system is increased by the fact that photochemistry can also be used to isomerize the α,β-unsaturated ester products (Scheme 3). Thus, irradiation of the enoates through quartz (254 nm lamps) gave β,γ-unsaturated esters as expected, whereas under the same conditions the enedioates, derived from the disubstituted acetylenes, underwent a novel double isomerization. Initially these reactions were carried out conventionally[11] in the presence of a trace of amine, however, it subsequently became clear that this is not required in many cases.

Thus, in general terms, this photomediated reaction of cycloalkanes with alkynes constitutes a novel way of carrying out a fundamentally important process, the functionalisation of a saturated hydrocarbon. Our



Scheme 2.



Scheme 3.

experiments suggest that the process is synthetically useful for alkynes with electron-withdrawing substituents, and for hydrocarbons, which for reasons of symmetry or reactivity, give a unique radical following hydrogen abstraction. It is particularly attractive from the green/clean chemistry point of view as it can utilise solar radiation and a potentially recyclable polymer-bound photomediator. Further synthetic and mechanistic studies relating to these aspects of the reaction, and to the basic reaction itself, are currently under way.

Acknowledgements

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