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CONSECUTIVE DIELS-ALDER- MICHAEL ADDITION - 1,3-DIPOLAR CYCLOADDITION PROCESSES

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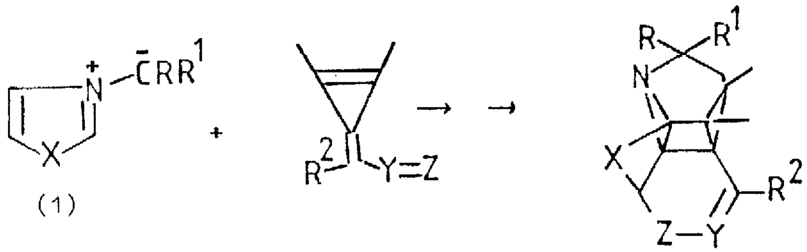
Abstract. The first examples of a new consecutive Diels-Alder - Michael addition- 1,3-dipolar cycloaddition process are described. The 1,3-dipolar cycloaddition step involves a nitrone generated in situ from an oxime and an electronegative olefin. The overall process results in the creation of six new stereocentres.

The Diels-Alder and 1,3-dipolar cycloaddition reactions are widely employed in synthesis because of their pronounced regio- and stereoselectivity. When used in their intramolecular versions[1,2] they provide powerful synthetic methodology for the construction of fused or bridged carbo- and/or hetero-cyclic systems. Each reaction has the capacity for generating up to four chiral centres in a single step, i.e. they are processes in which there is a substantial increase in molecular complexity.[3] The combination of these two reactions in a tandem process would thus constitute exceptionally powerful synthetic methodology.

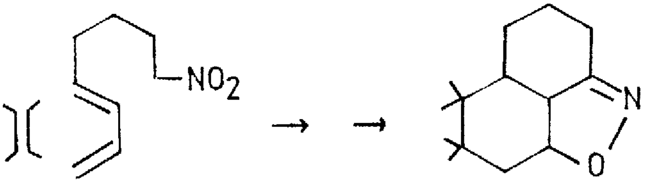
To date there have been very few attempts to achieve this tandem or sequential combination and no proper analysis of the process. We have found only three reports of such processes, i.e. (1) → (2)[4], (3) → (4)[5], and (5) → (6)[6]. Of these (1) → (2) is somewhat esoteric and unlikely to have general synthetic appeal and (3) → (4) is not a tandem process in that the Diels-Alder adduct requires modification of the nitro group to a nitrile oxide before the second stage can proceed. The reaction (5) → (6) is a good example of the tandem process but proceeds in moderate yield or gives a mixture of regioisomers. In the example (1) → (2) the 1,3-dipolar cycloaddition precedes the Diels-Alder reaction whilst in the latter two cases the Diels-Alder reaction precedes the 1,3-dipolar cycloaddition and the double bond of the resulting cyclohexene functions as the dipolarophile. Our work is also concerned with this latter process.

There are potentially four broad synthetic variants of this latter tandem Diels-Alder - 1,3-dipolar cycloaddition process (Table).



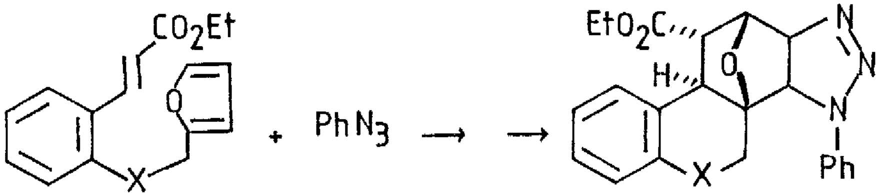
(1)

(2)



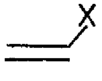
(3)

(4)

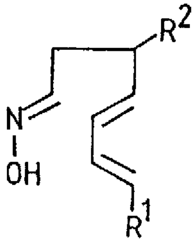


(5)

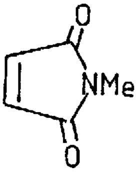
(6)



(7) a. X = SO_2Ph
b. X = CO_2CH_2Ph
c. X = COMe



(8) a. $R^1 = R^2 = H$
b. $R^1 = H$, $R^2 = Me$
c. $R^1 = CO_2Me$, $R^2 = H$



(9)

Table. Synthetic Variants of the Tandem Diels-Alder-1,3-Dipolar Cycloaddition Reaction

Class	Diels-Alder Reaction	1,3-Dipolar Cycloaddition
1	intermolecular	intermolecular
2	intermolecular	intramolecular
3	intramolecular	intermolecular
4	intramolecular	intramolecular

A potentially major problem in the synthetic realisation of classes 1-4 (Table) is the necessity to achieve chemospecific discrimination between dienophile and dipolarophile. The tandem process (5) ⟶ (6) represents an example of a class 3 process. We now report several examples of class 2 processes based on our recently reported powerful oxime methodology.[7] This methodology generates a nitrone in situ by Michael addition of an oxime, via the nitrogen lone pair, to a suitable electronegative olefin. Thus our examples constitute yet more powerful synthetic methodology in that they comprise conseceutive Diels-Alder - Michael addition- 1,3-dipolar cycloaddition processes.

Heating a mixture of the Michael acceptor (7a-c), diene oxime (8a), and N-methylmaleimide (9) in xylene at 80°C for 2-5h results in a chemospecific Diels-Alder reaction giving (10). If the temperature is then raised to ca. 140°C for a further 5-15h Michael addition occurs giving (11) followed by a 1,3-dipolar cycloaddition reaction giving (12a-c) in ca. 60% yield. The stereochemistry of (12a-c) was established by n.O.e. studies at 400MHz.[8] The stereochemistry of (12a-c) could arise either from an exo-addition of the Z-nitrone or an endo-addition of the E-nitrone. A study of molecular models indicates the former to be more likely. Our previous studies on oxime cycloadditions showed syn $\rightleftarrows$ anti oxime interconversion to be facile in boiling xylene.[7]

Preliminary studies of analogous reactions with diene oxime (8b) show the initial Diels-Alder reaction to be substantially slower allowing side reactions to intervene. Diene oximes (8c) and (13) both undergo clean Diels-Alder reactions but the oxime cycloaddition step does not occur to any significant extent in xylene at 140°C.

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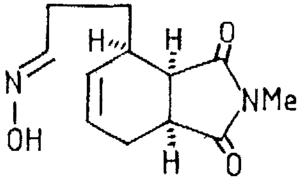
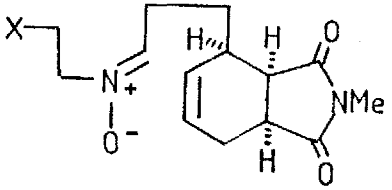
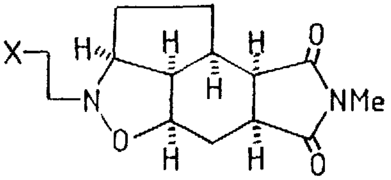


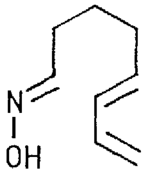
(10)



(11)



(12) a. X = SO_2Ph
b. X = CO_2CH_2Ph
c. X = COMe



(13)

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