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# REGIO- AND STEREO-SPECIFIC CLASS 2 TANDEM MICHAEL ADDITION-CYCLOADDITION REACTIONS OF OXIMES

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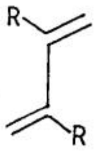
Abstract. Oximes react regio- and stereo-specifically with 1,3- , 1,4- and 1,5-dienes bearing electronegative substituents via a tandem Michael addition-1,3-dipolar cycloaddition process to give bridged ring cycloadducts in good yield.

Recently[1,2] we described a new tandem Michael addition 1,3-dipolar cycloaddition process of oximes and identified four broad synthetic variants of the tandem process. Examples of all four classes of tandem process were described[1,2] and the tandem processes were shown to constitute extremely powerful and flexible methodology for the construction of carbon-carbon bonds, and bridged- and fused-ring systems.

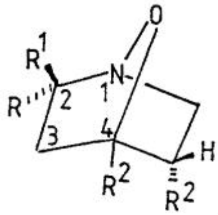
We identified the class 2 synthetic variant (intermolecular Michael addition-intramolecular 1,3-dipolar cycloaddition) as being particularly valuable in synthesis because it can be achieved in two distinct ways.[1] Thus the dipolarophile can be incorporated into the oxime, or the Michael acceptor and dipolarophile can be combined in the same substrate. Thus 1,$\omega$-dienes of various types potentially provide a wide spectrum of synthetic possibilities. The recent report[3] of examples of class 2 processes prompts us to report further developments of this chemistry.

The 1,3-dienes (1a) and (1b) react regio- and stereo-specifically with benzaldehyde oxime, and cyclohexanone and cyclopentanone oximes in boiling xylene (for 1a) or boiling acetonitrile (for 1b) to give a single 1:1 adduct in each case which could be formulated as (2) or (3). P.m.r. studies of the 1:1 adducts were inconclusive but $^{13}$C n.m.r. clearly favour (2), e.g. the chemical shift of the bridgehead tetrasubstituted carbon atom C(4) in (2b) occurs at 92.3Hz. The calculated chemical shift of C(4) in (2) is 93.4Hz whilst the calculated chemical shift for the analogous bridgehead carbon atom in (3) is 71.3Hz.[4,5] A single crystal X-ray structure determination shows the benzaldehyde oxime adduct of (1a) has structure (2c). Cycloadducts (2a-c) and (2d,e) were obtained from the appropriate oxime, and (1a) and (1b) respectively, in essentially quantitative yield. Padwa observed that diene (1c) reacts with oximes in an analogous manner.[3]

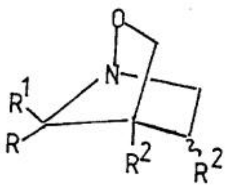
Previously[1] we reported that the 1,3-diene (4a) reacts with cyclohexanone oxime to give a mixture of bridged ring cycloadducts. We now report that the appropriate aryl oximes and (4a) react (xylene, 140°C)



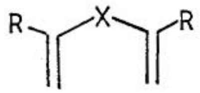
(1) a. $R=P(O)Ph_2$
b. $R=CO_2Me$
c. $R=SO_2Ph$



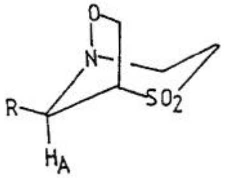
(2) a. $R,R^1=(CH_2)_4,R^2=P(O)Ph_2$
b. $R,R^1=(CH_2)_5,R^2=P(O)Ph_2$
c. $R=H,R^1=Ph,R^2=P(O)Ph_2$
d. $R,R^1=(CH_2)_5,R^2=CO_2Me$
e. $R=H,R^1=Ph,R^2=CO_2Me$



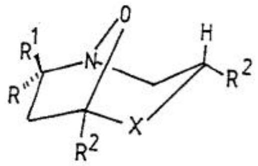
(3)



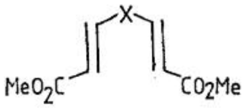
(4) a. $R=H,X=SO_2$
b. $R=H,X=P(O)Ph$
c. $R=CO_2Et,X=CH_2$



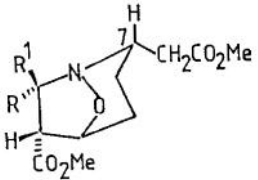
(5) a. R=Ph
b. $R=\underline{p}\text{-}MeOC_6H_4$
c. $R=\underline{p}\text{-}O_2NC_6H_4$



(6) a. $R,R^1=(CH_2)_5,$
$R^2=H,X=P(O)Ph$
b. $R,R^1=(CH_2)_5,$
$R^2=CO_2Et,X=CH_2$



(7) $X=(CH_2)_2$



(8) a. $R,R^1=(CH_2)_5$
b. $R=Ph,R^1=H$

regio- and stereo-specifically to give (5a-c) in ca. 60% isolated yield. p-Nitrobenzaldehyde oxime reacts noticeably slower (34h) than p-methoxybenzaldehyde oxime (7h). In the p.m.r. spectra of (5a-c) the signal for $H_A$ appears as a singlet at 5.1-5.8. In contrast, the 1,3-dienes (4b) and (4c) react with cyclohexanone oxime (xylene, 140°C) to give (6a) and (6b) respectively in essentially quantitative yield. The differing regiochemistry in the latter cases is presumably associated with geometrical factors arising from the size of the X group in (4) and the CXC bond angle.

The 1,5-diene (7) reacts regio- and stereo-specifically with cyclohexanone oxime (xylene, 140°, 24h) to give (8a) (80% yield, 60% conversion). The analogous reaction with benzaldehyde oxime gives two major isomers which are C(7) epimers of (8b) together with trace amounts of two other isomers.

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4. We thank Dr Thomas, Roche Products, Welwyn Garden, for these measurements and for helpful discussions.
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