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The Synthesis of 1,2,7,11b-Tetrahydroisoxazolo[2,3-*d*][1,4]benzodiazepin-6(5H)-ones and 1,3,3a,9b-Tetrahydroisoxazolo[4,3-*c*]quinolin-4(5H)-ones

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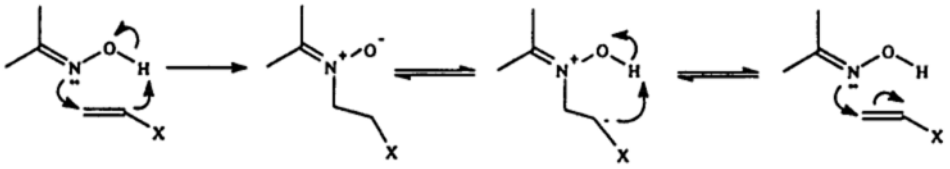
Abstract: The reaction of various ethyl 3-[[2-(1-hydroxyiminoalkyl)phenyl]carbamoyl]acrylates (2) with electron deficient olefins proceeds *via* a sequential dipole formation, dipolar cycloaddition sequence to furnish the tetrahydroisoxazolo[2,3-*d*][1,4]benzodiazepin-6(5H)-ones and tetrahydroisoxazolo[4,3-*c*]quinolin-4(5H)-ones (4) and (6). The product distribution reflects the nature of the reacting olefin and the position and extent of substitution on the acrylate moiety.

The biological activity of variously substituted benzodiazepines is well established, perhaps most significant is their clinical success as powerful, mild anti-anxiety drugs. When a third ring is annealed to the *a*-, *c*-, or *d*- edge the tricyclic adduct may show sedative activities that are up to an order of magnitude greater than their parent system[1]. This paper reports an investigation into the synthesis of the tetrahydroisoxazolo[2,3-*d*][1,4]benzodiazepin-6(5H)-one ring system (4), a tricyclic skeleton first prepared in 1982[1].

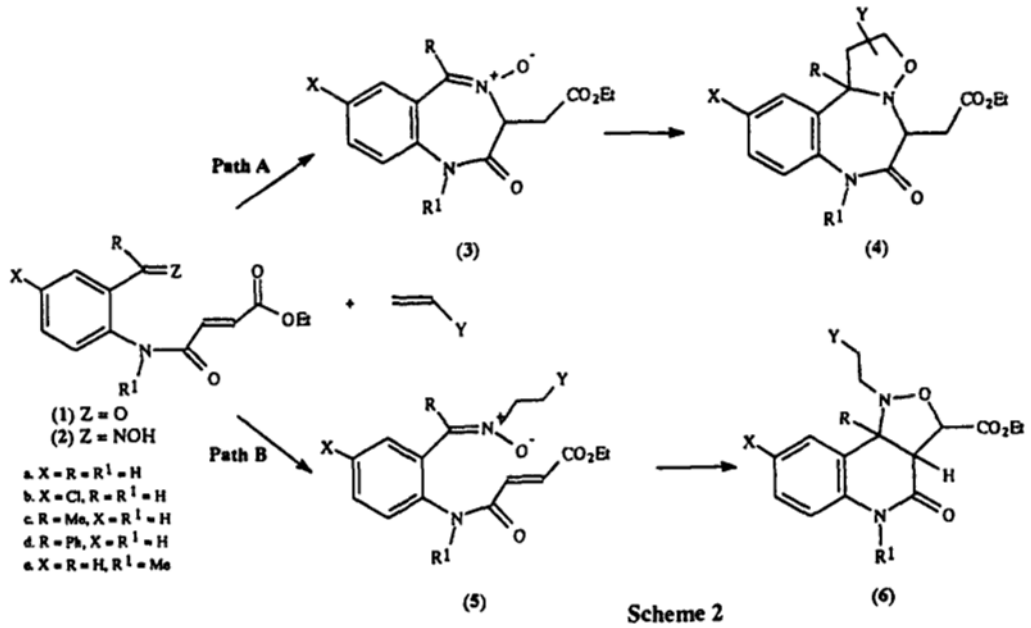
We envisaged that transformation of functionalised oximes, such as (2) by a "one-pot" dipole formation-cycloaddition sequence would represent a novel synthetic approach to the desired ring system. Oximes of aldehydes (and ketones) bearing a γ- or δ-unsaturated substituent are known to undergo thermal conversion to 5- and 6-membered cyclic nitrones respectively[2]. The procedure involving a 1,3-azaprotio cyclotransfer process, described by Grigg *et al*, has not been demonstrated for ε-unsaturated oximes. However Masuoka and coworkers have reported on the synthesis of medium sized heterocycles, benzoxazepines, benzoxazocines and benzoxazonines by an intramolecular Michael addition reaction[3] and since the 1,3-azaprotio cyclotransfer process is theoretically the concerted equivalent of the Michael addition reaction[2] (Scheme 1) we propose (2) ought to partake in a 7-*exo-trig* cyclization to furnish the 7-membered cyclic dipole (3)[4] (Scheme 2). *In situ* trapping of the dipolar species with suitable dipolarophiles ought to lead to the tetrahydroisoxazolo[2,3-*d*][1,4]benzodiazepin-6(5H)-one ring system.



1,3-AZAPROTIO CYCLOTRANSFER FORMAL MICHAEL ADDITION

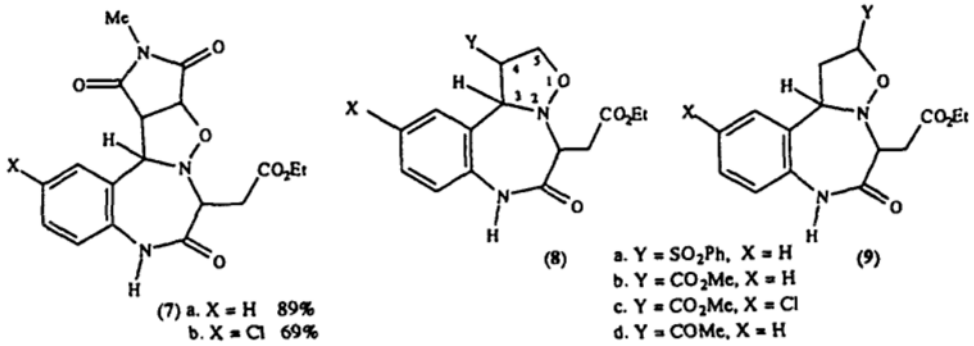
Scheme 1

Evidently the question of chemoselectivity arises since two modes of reaction are conceptually possible, path A and path B (Scheme 2). Only path A (intramolecular dipole formation/intermolecular cycloaddition) can lead to the targeted ring system, however path B (intermolecular dipole formation/ intramolecular cycloaddition) can furnish the relatively rare tetrahydroisoxazolo[4,3-*c*]quinolin-4(5H)-ones (6)[5]. The lower energy path will depend on the choice of olefin and on the nature and position of any substituents on the oxime.

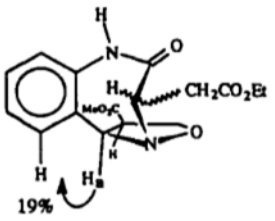


Scheme 2

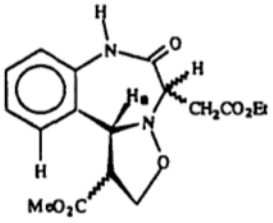
Aldoximes (**2a,b**) are easily prepared from their parent 2-aminobenzoic acids, reduction to the alcohol followed by reaction with fumaric acid chloride monoethyl ester gives the corresponding amides. Oxidation of the primary alcohol functionality affords the desired aldehydes (**1**) which are readily oximated. When the oximes (**2a,b**) are reacted with an equimolar amount of N-methylmaleimide (xylene, 140 °C, 8 h), phenyl vinyl sulphone or methyl acrylate (toluene, 110 °C, 24 h) reaction proceeds exclusively *via* path A. Each oxime reacts with N-methylmaleimide to give a single stereoisomeric cycloadduct (**7**) in excellent yield. Phenyl vinyl sulphone and methyl acrylate react with (**2a**) affording mixtures of the regioisomeric 4- and 5-substituted isoxazolidines (**8a,b**) and (**9a,b**) in a 7:2 and 3:1 ratio respectively. Examination of the n.O.e. difference spectra of the adducts (**8b**) and (**9b**) suggest these molecules adopt the folded conformation [shown for (**8b**)], the alternative extended conformation would be incompatible with the observed 19% enhancement on the *o*-ArH on irradiation of the benzylic proton H_a. Reacting (**2b**) with methyl acrylate furnishes a single regio- and stereo-isomeric adduct, (**8c**).



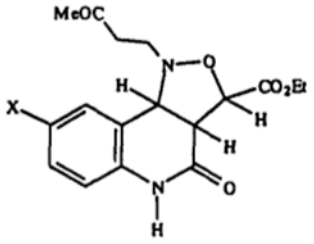
When methyl vinyl ketone is used in this reaction surprising results are obtained. Thus heating oxime (**2a**) with an equivalent amount of methyl vinyl ketone (toluene, 110 °C, 18 h) results in the formation of two different molecular frameworks. The main product, the tetrahydroisoxazolo[4,3-*c*]quinolin-4(5H)-one (**10a**) (70%) arises from reaction *via* path B and the 4-substituted isoxazolo[2,3-*d*][1,4]benzodiazepin-6(5H)-one (**8d**), obtained in just 9% yield arises *via* path A (Scheme 2). Oxime (**2b**) reacts regio- and chemo-specifically to furnish (**10b**) as the sole reaction product.



Folded conformation



Extended conformation

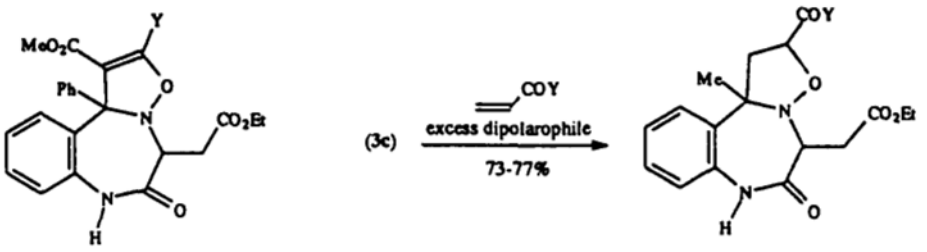


(**10**) a. X = H
b. X = Cl

These observations may be rationalised on consideration of the relative electrophilicity of a range of activated vinyl compounds toward nucleophilic attack which falls off in the sequence COR>SO_2R> CO_2R>$CONH_2$>CONHR[6]. Extrapolation of this data suggests "Michael type" addition to an unsaturated ketone or sulphone should be prevalent over addition to an unsaturated ester or amide. Indeed we have found this to be the case when all reactions are taking place in an intermolecular sense[7,8]. In the current situation competition is between an intramolecular addition (*pseudo* high concentration) to an unsaturated ester and intermolecular addition to an unsaturated sulphone or ketone. Analysis of the reaction product/s shows intramolecular addition to an unsaturated ester moiety is more favourable than intermolecular addition to a sulphone but is the less favoured reaction in the presence of an unsaturated ketone. Thus the 1-acyl derivative (**8d**) can only be prepared in high yield by a two step procedure involving pre-formation of the nitrone (**3a**). Simply heating oxime (**2a**) generates (**3a**) in quantitative yield. Trapping of the isolated dipole with methyl vinyl ketone furnishes the appropriately substituted tricyclic adduct. Indeed the two step reaction represents an alternative route to all the above mentioned isoxazolobenzodiazepine molecules, chemical yields and product distribution parallels that seen for the "one-pot" process.

The ketone derivatives (**1c,d**) behave quite differently from their aldehyde analogues. Under standard oximation conditions cyclic nitrones (**3c,d**) are formed in good yield, no oxime is observed. These dipoles are efficiently trapped, regio- and stereo-specifically with acetylenic dipolarophiles (dimethyl acetylenedicarboxylate and methyl propiolate) furnishing thermally labile dihydroisoxazolo-benzodiazepine adducts (**11**). Ring contraction of these primary products to quinoxalinones is observed upon heating in boiling ethanol[9]. In contrast trapping of (**3c**) with olefinic moieties could only be achieved by employing a huge excess of dipolarophile, indeed (**12a,b**) result following heating in boiling methyl acrylate and methyl vinyl ketone respectively.

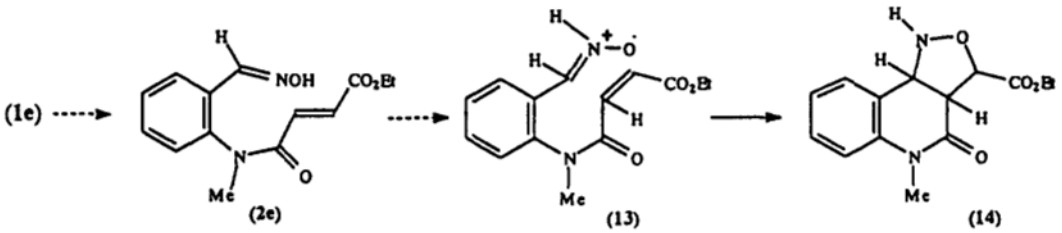
In order to prepare isoxazolobenzodiazepines with a substituent on N-1, the aldehyde (**1e**) was prepared. Surprisingly when oximation of this substrate was attempted neither the expected oxime (**2e**) nor the dipole (**3e**) resulted, instead the product of reaction was the isoxazoloquinolinone (**14**). The formation of (**14**) can be explained by assuming the initially formed oxime (**2e**) tautomerises to the acyclic



(11) Y = H, CO_2Me

(12) a. Y = OMe
b. Y = Me

dipole (13) which undergoes a sequential intramolecular cycloaddition to give the product in good yield. Such 1,2-protropy whilst theoretically a facile process for oximes is only observed in very special cases[10]



(2e) (13) (14)

Work is actively continuing in this area.

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