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A New Selective Reduction of Nitroalkenes into Enamides

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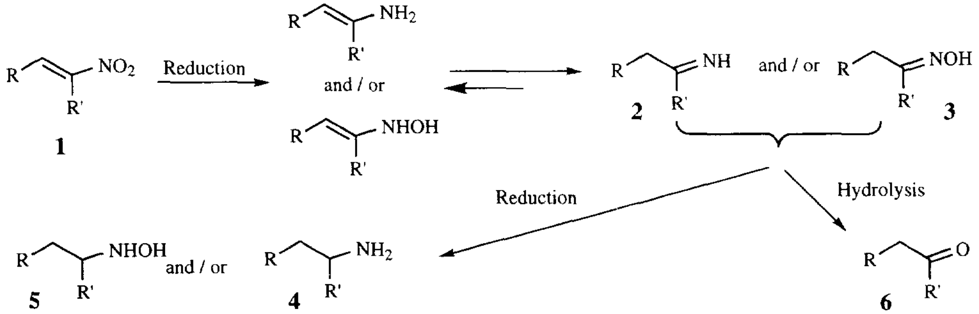
Abstract : Conjugated nitroalkenes can be reduced into enamides by a combination of iron powder, a carboxylic acid, and the corresponding anhydride.

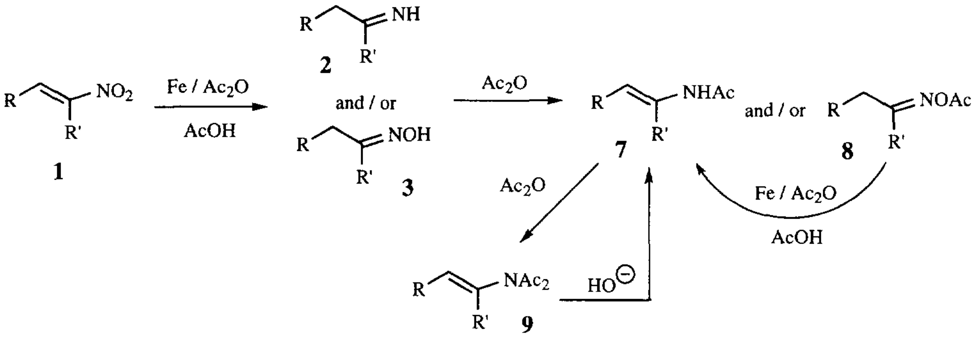
The reduction of nitro compounds is an important and widely used transformation in organic synthesis.[1] Complete reduction provides amines or anilines in the case of aromatic nitro derivatives. Under certain conditions the reduction may be halted at the hydroxylamine stage, especially when aromatic or tertiary nitro groups are used as substrates. Some reagents are capable of effecting partial reduction of aliphatic nitro groups into oximes,[2] and these in turn may be cleaved into imines,[2] which upon hydrolysis give the corresponding carbonyl derivatives. The reduction of conjugated nitroalkenes such as nitrostyrenes constitutes a special problem.[1,3] In addition to the above general transformations, it is possible to reduce the double bond (usually with borohydride) while keeping the nitro group intact.[3] The converse however is not as easily accomplished. We now describe a simple and practical procedure for converting nitrostyrenes and other unsaturated nitro derivatives into enamides, a transformation that was needed in connection with another project.



Scheme 1

As summarized in scheme 1 above, the difficulty in reducing the nitro group in conjugated nitroalkenes **1** with common reducing agents is that the reaction can lead to an enamine or to an unsaturated hydroxylamine, and these are in a generally unfavourable equilibrium with the respective imine or oxime.[4] Depending on the strength of the reducing agent, further reduction to amine **4** or hydroxylamine **5** can take place and, if water is present, hydrolysis to a carbonyl derivative **6** is also possible. All these species can interact in the medium to give complex mixtures, especially with terminal nitroalkenes (i.e. R' = H). It seemed conceivable that if reduction is carried out in the presence of an anhydride, then it should be possible to capture the enamine / imine under the guise of an enamide and thus limit considerably the extent of unwanted side reactions. The reducing reagent must be compatible with the presence of an anhydride and sufficiently mild to allow survival of the enamide.

Some years ago, we used a combination of iron powder and acetic anhydride to convert oximes, via the oxime acetate formed *in situ*, into ene-acetamides or ene-acetimides depending on the conditions.[5] We therefore reasoned that if iron powder / acetic acid could reduce a conjugated nitroalkene either to the level of the oxime **3** or to that of the imine **2** then, in the presence of acetic anhydride, both would be trapped. The latter would lead directly to the desired enamide **7** whereas the former would give an oxime acetate **8** which in turn will be reduced further to the same enamide, as outlined in Scheme 2. Moreover, the presence of acetic anhydride would prevent any premature hydrolysis from occurring at any stage. The enamide may, totally or in part, be acetylated to the enimide **9** but this is easily reversed by treatment with methanolic sodium or potassium hydroxide, or even by simple adsorption on alumina.[5,6]

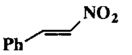
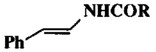
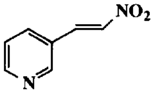
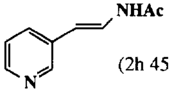
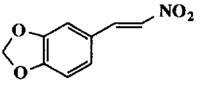
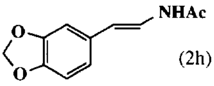
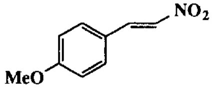
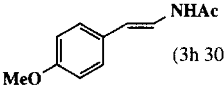
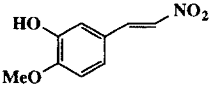
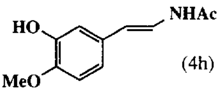
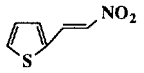
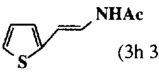
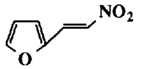
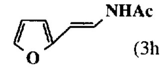
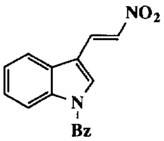
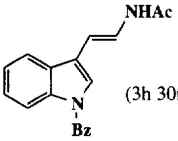
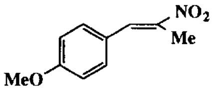
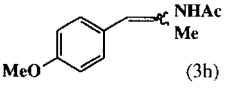
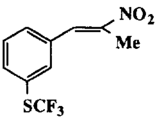
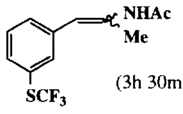
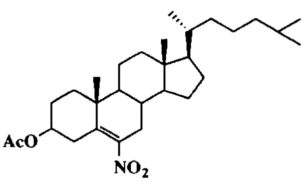
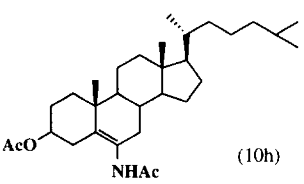


Scheme 2

These considerations were readily reduced to practice. Heating a mixture of β-nitrostyrene, acetic acid, acetic anhydride, and iron powder gave as major product the expected enamide in reasonable yield (55%). The crude residue was treated with base (sodium or potassium hydroxide) to cleave variable amounts of enimide also produced in the medium.[7] A number of other nitroalkenes were reduced in the same manner, as illustrated by the examples collected in the Table. The yields are generally good, even though none has been optimized. In some cases a significant amount of the cis isomer of the enamide could be isolated (entries 6,7,8). The procedure is compatible with a variety of substituents on the aromatic rings in the case of β-nitrostyrene derivatives and various heteroaromatic rings such as furan, thiophene, pyridine, or even indole are tolerated. Purely aliphatic nitroalkenes are reduced more slowly (entry 11) but the scope of the method in this area remains to be explored more extensively. Obviously, the process is not limited to acetamide derivatives; other congeners may be obtained by replacing acetic acid and its anhydride with other combinations of carboxylic acid and anhydride. As illustrated by the example in entry 1b, an ene-propionamide can be prepared using a combination of propionic acid / propionic anhydride.

This approach provides a simple, inexpensive, and easily scalable entry into variously substituted aromatic and aliphatic enamides. Such enamides have been prepared previously by way of a Curtius rearrangement on the corresponding β-arylacrylic acid,[8] a rather hazardous route when performed on a large scale, and by copper induced decarboxylation of α–amidoacrylates.[9] More tedious or less general synthetic schemes have also been proposed.[10]

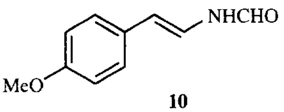
Table 1: Reduction of nitroalkenes.

Entry	Nitroalkene	Reaction product (Reaction time)	Yield
1		 a) R=Me (2h) b) R=Et (3h)	a) 67% b) 60%
2		 (2h 45m)	65%
3		 (2h)	62%
4		 (3h 30m)	60%
5		 (4h)	58%
6		 (3h 30m)	73%[a]
7		 (3h)	81%[b]
8		 (3h 30m)	69%[c]
9		 (3h)	75%[d]
10		 (3h 30m)	75%[d]
11		 (10h)	70%

a: Includes 8% Z isomer. b: Includes 18% Z isomer. c: Includes 12% Z isomer. d: Approximately a 2:1 mixture of E:Z isomers (NMR assignements by analogy with observations in reference 10f).

That the reaction works so well with β-nitrostyrenes *unsubstituted at the α-position* is remarkable. The reduction of such substrates by other methods is in general problematic[1,3] since highly reactive N-unsubstituted aldimines (**2**, R'= H) can be produced and these undergo all manner of adverse condensation reactions. The corresponding aldoximes (i.e. **3**, R'= H) and even more so their acetates are prone to dehydration into nitriles. Yet good yields of the respective enamides are nevertheless obtained.

Enamides constructed by the present procedure are interesting in their own right but can also serve as starting materials for more elaborate substances. It is worth noting that some members of this family have been isolated from natural sources and many exhibit an interesting biological activity.[8,11,12] For example, tuberin **10** and erbstatin **11** possess antibacterial activity,[12] and N-acetyl-1,2-didehydrodopamine **12** is suspected of being a causative agent in the sclerotization of insect cuticle.[13] The obtention of the enamide in entry 5 represents a formal synthesis of the latter substance since the demethylation (using BBr_3) has already been described in the literature.[10a]



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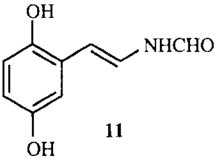

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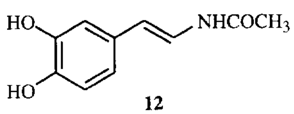

12

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7. A typical experimental procedure is as follows: A suspension of iron powder (60 mmol) in acetic anhydride (6 ml) and acetic acid (0.3 ml) was heated to reflux under an argon atmosphere for 30 minutes and the nitroalkene (3 mmol) was then added in portions over 1 hour. After heating for a further 2-5 hours until total consumption of the starting material (TLC), the mixture was cooled, diluted carefully with methanol and filtered. The filtrate was evaporated and the residue taken up in a little methanol and the pH adjusted to about 12-14 (pH indicator paper) using methanolic KOH. Filtration through celite followed by removal of the solvent and purification of the residue by chromatography on silica gel finally afforded the respective enamides in the yields given in the table.
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