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EFFICIENT CHEMOSELECTIVE REDUCTION OF 3-SUBSTITUTED COUMARINS UTILIZING *ortho*-PHENYLENEDIAMINE AND BENZALDEHYDE

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Abstract – 2-Phenylbenzimidazoline, generated *in situ* from *ortho*-phenylenediamine and benzaldehyde**,** is an effective reagent to achieve the chemoselective reduction of the styrenic double bond in 3-substituted coumarins, which takes place in high yield.

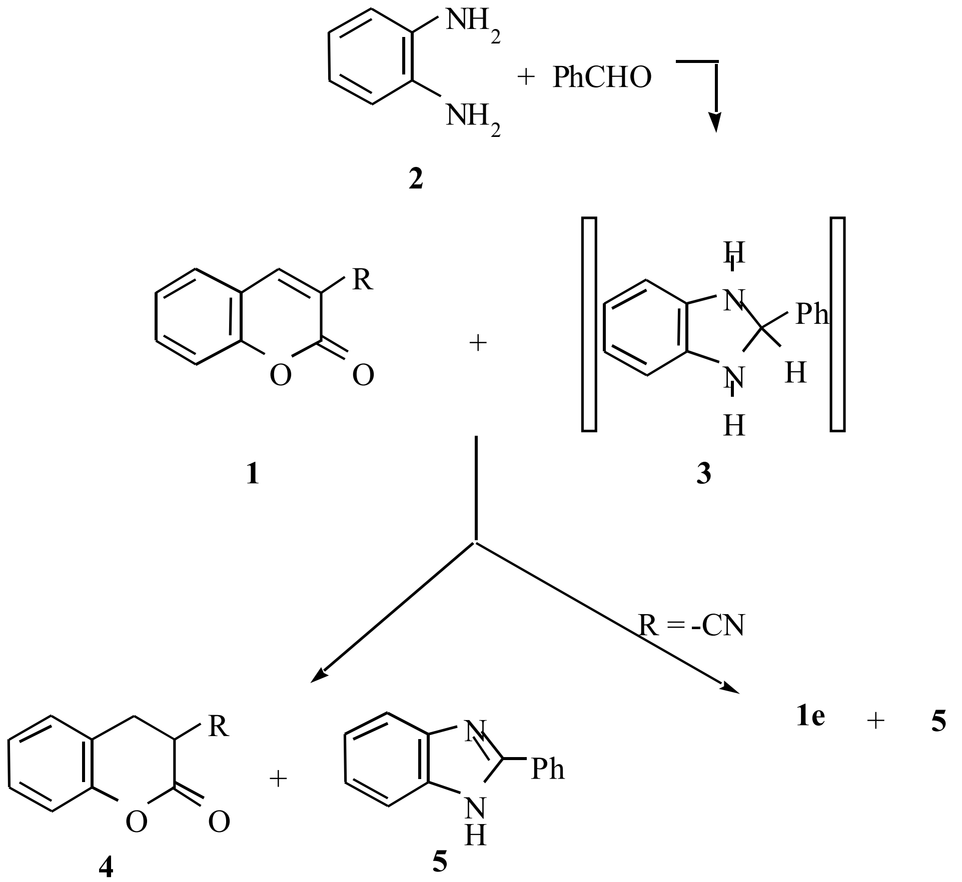
The reaction of *ortho*-phenylenediamine with electron deficient olefins in the presence of the appropriate arylaldehyde is one of the best methods of chemoselective reduction of double C-C bonds conjugated with electron withdrawing groups.[1] This reaction occurs by way of *in situ* formation of 2-phenylbenzimidazoline, which oxidises to benzimidazole and releases dihydrogen.[2] The hydrogen transfer mechanism seems to depend on the stereoelectronic properties of the substrate. For example, a two step ionic process has been proposed in the reduction of nitro- and cyanoolefins or of an α,β-unsaturated ester,[3] while a SET mechanism has been hypothesised in the case of 4-arylmethylene isoxazol- or pyrazol-5-ones.[4] Nevertheless, the synthetic usefulness of this reaction has been demonstrated in both cases.

We attempted to extend this efficient and mild reductive procedure to endocyclic double C-C bonds. In this note we report the results obtained with coumarins (**1**) substituted with electron withdrawing groups in 3 position.

o-Phenylenediamine (**2**) reacted with coumarins (**1**)[5] in the presence of benzaldehyde and in the conditions set up beforehand.[6] The benzimidazoline (**3**), generated in ethanol or THF solution, reacted with **1** giving the expected dihydro derivatives (**4a-d**) in high yield,[7] and the 2-phenylbenzimidazole (**5**)[8] quantitatively (Scheme 1). Products deriving from a preferential attack of the diamine on the C-4 of the lactones (**1**) were never isolated.[9] In the case of **1e** the coumarin substrate does not react, although the benzimidazole (**5**) is recovered. This proves that benzimidazoline (**4**) was formed under the described conditions.

The structure of the dihydrocumarins (**4a**, **b**, **d**) was assigned by comparing analytical and spectral data with authentic samples prepared by other means.[10] **4c** was assigned by spectroscopic analogy with **4a**, **b**, **d**.

Considering the unequivocal intermediacy of benzimidazoline (**3**) as hydrogen donor , the way in which the olefin site becomes saturated still needs to be clarified. The unsuccessful reaction of the coumarin (**1e)** and the unobserved formation of reductive dimer by-products, exclude the two paths discussed above.

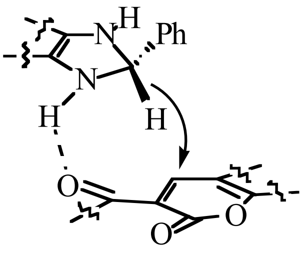


R	-COMe	-COPh	$-CO_2Me$	$-CO_2Et$	-CN
	a	**b**	**c**	**d**	**e**

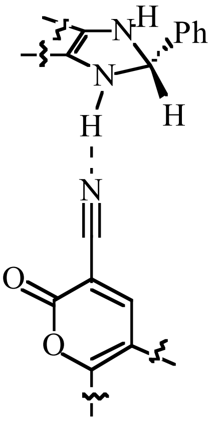
Thus, it may be assumed that the hydrogen transfer to the multiple bond of the 3-substituted lactones (**1**) could take place through **A**.

In **A**, as a consequence of the hydrogen bond between the carbonyl oxygen at the 3-position and one of the NH groups, benzimidazoline and coumarin are in such a position as to reasonably allow hydrogen transfer to occur.

Coumarins (**1**) (R = H and R = *p*-$NO_2C_6H_4$), as well as **1e**, did not undergo any reduction under the same reaction conditions and could be recovered at the end of the reaction together with benzimidazole (**5**). Association such as **A** was prevented in the case of 3-cyanocoumarin (**1e**) shown in **B**. The hydrogen transfer can not take place from this configuration. In addition, the conformation of benzimidazoline would make the nitrogen lone pairs in antiperiplanar position to the Csp3-H bond. This appears to contribute to weaken the C-H bond, which generates a hydride ion.



A



B

In conclusion, we have reported a new efficient method for the chemoselective reduction of coumarins. The present method is superior to other more sophisticated methods[11] in that it offers the ready access to the reducing agents, operational simplicity, mild conditions, and high yields of dihydro coumarine derivatives.

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4. The proposed radical mechanism for the 4-arylmethyleneazolones is the only one that can explain the formation of products derived from a reductive dimerisation and the non-heterocyclic ring opening followed by rearrangements (ref. 1). An example is the reduction, under classic conditions, of arylmethyleneisoxazol-5-ones: G. Shaw, *J. Chem. Soc.*, 1950, 720.

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7. General procedure: An EtOH (or THF) solution of diamine (**2**) (432 mg, 4.0 mmol) was added dropwise over 20 min to a refluxing mixture of **1** (4.0 mmol) and benzaldehyde (655 mg, 5.5 mmol) in EtOH (50 mL). Stirring was continued for a further 0.5 h and then the reaction mixture was evapored to give an oil residue which was neutralised with HCl 10% (30 mL). The acidic aqueous suspension was then extracted with ether (3x30 mL) and the combined ether extracts were washed with water (70 mL) and dried on sodium sulfate. Filtration followed from evaporation of the filtrate solvent gave an oil which was crystallized from ethanol or chromatographed on a silica gel (with chloroform as eluent) to yield the dihydro derivatives (**4**). The acidic solution with benzimidazole hydrochloride in suspension was made alkaline with 10% sodium hydroxide to give benzimidazole (**5**). The following products have been isolated: **4a** from coumarin (**1a**) in 85% yield, mp 75°C (lit.,[7] mp 72-85°C); **4b** from **1b** in 92% yield, mp 99°C (lit.,[7] mp 102°C); **4c** from **1c** in 85% yield, mp 91°C. Anal. Calcd for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found C, 63.99; H, 4.85. IR (Nujol): ν_{max}=1772 and 1738 cm^{-1}. ^1H NMR ($CDCl_3$): δ= 4.05 (3H, s, OCH_3), 3.19 (1H, dd, *J* = 6.5, 16.1 Hz), 3.45 (1H, dd, *J* = 8.9, 16.1 Hz), 3.79 (1H, dd, *J* = 6.5, 8.9 Hz), 6.8-7.5 (4H, m). **4d** from **1d** in 81% yield, mp 51°C (lit.,[7] mp 51-52.5°C). From **1e** and **1** (R= H or 4-nitrophenyl) no corresponding derivative (**4**) was obtained, but the starting coumarin and benzimidazole (**5**).
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