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AN EFFICIENT PREPARATION OF 4-ARYLMETHYLISOXAZOL-5-ONES BY SELECTIVE REDUCTION OF THE 4-ARYLMETHYLENEISOXAZOL-5-ONES

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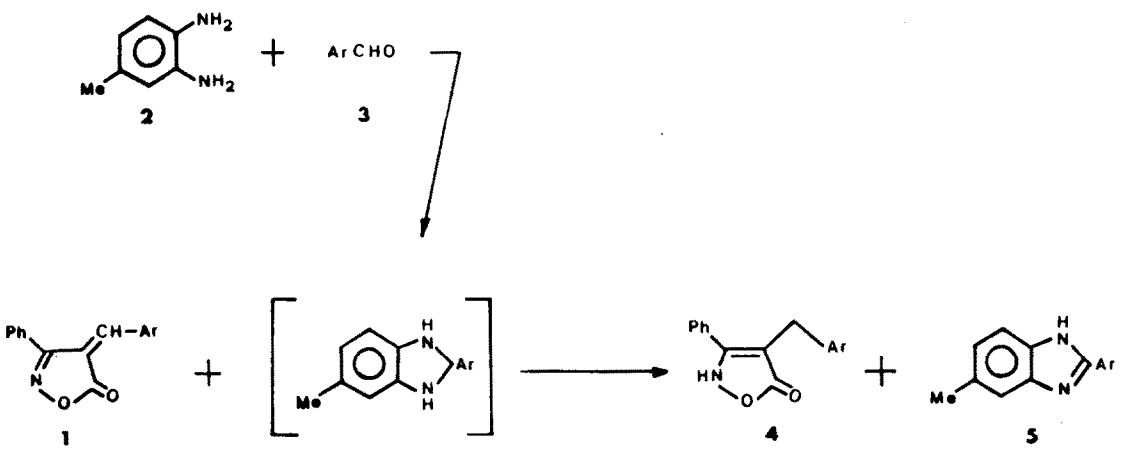
Summary: An efficient selective reduction of the exocyclic double bond of the 4-arylmethyleneisoxazol-5-ones with o-phenylenediamines and aldehydes is described. 4-arylmethylisoxazol-5-ones are produced in high yields together with comparable quantities of benzimidazoles.

The literature method[1,2] for the synthesis of 4-arylmethylisoxazol-5--ones is generally long and inefficient and the only practical way for their preparation involves the reduction of the exocyclic double bond of the readily available 4-arylmethyleneisoxazol-5-ones.However, since unavoidable disruption of the isoxazolone nucleus also occurs, the hitherto reported reductive procedures[3] are not entirely satisfactory.

We now find that a facile and selective reduction of the above substrates to the corresponding 4-arylmethyl derivatives can be accomplished in high yield by their reaction with o-phenylenediamines and aldehydes. This is due to the well-known reducing action of the hydrogen donor benzimidazoline intermediate, which is rapidly oxidized to benzimidazole[4].

Here we report our results with a number of 4-arylmethylene-3-phenyliso-xazol-5-ones (1), 3,4-diaminotoluene (2) and the appropriate arylaldehyde (3).

Diamine (2) (0.01 mol) in ethanol (20 ml) was added dropwise over 20 min to a stirred solution (50 ml) of aryliden derivative (1) (0.01 mol) and aldehyde (3) (0.01 mol) in ethanol under reflux. Stirring was continued for a further 30 min and then the reaction mixture was evaporated to give an oil residue which was treated with dilute hydrochloric acid (30 ml).



The reduced products (4) (see Table) were extracted with ether. The acidic solution was made alkaline with sodium hydroxide (10%) to give benzimidazoles (5)[5], in comparable yields with the products (4).

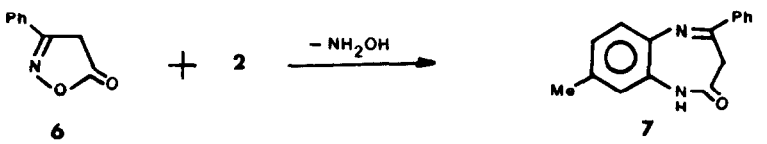
Table. Products (4). Yields and other relevant data.

	Ar	Yield %	M.p. t/°C	$\nu_{C=O}$ [α] cm^{-1}	Molecular formula [β]	^{1}H–NMR, δ (ppm) [γ] =C–CH$_2$–Ar
a	Ph	90	110	1685	$C_{16}H_{13}O_2N$	3.7 (s)
b	C_6H_4–Me (p)	88	111	1680	$C_{17}H_{15}O_2N$	3.67 (s)
c	C_6H_4–OMe (p)	88	110	1675	$C_{17}H_{15}O_3N$	3.7 (s) [ξ]
d	C_6H_4–OEt (o)	75	93	1810	$C_{18}H_{17}O_3N$	3.65 (s)
e	C_6H_2–(Me)$_3$ (o,p)	70	149	1800	$C_{19}H_{19}O_2N$	3.58 (s)

α- I.r. spectra were determined for Nujol mulls with a Pye Unicam SP 1000 spectrometer.
β- All products gave satisfactory microanalyses (C± 0.25; H± 0.10; N± 0.15%).
γ- Spectra were recorded on DMSO-d_6 solution with TMS as internal standard.
ξ- Overlapped by -OCH$_3$.

In agreement with the literature[6] and the data reported in the Table, we have depicted the products (4) only in the tautomeric form NH. However, for (4d) and (4e) the I.R. (Nujol mulls) carbonyl absorptions, at 1810 and 1800 cm^{-1} respectively, point out that, in these two cases, the CH form seems to be favoured[7].

Itoh et al.[8] reported a similar reduction of conjugated double bonds by reaction with o-phenylenediamine through a benzimidazoline intermediate. Using this procedure with our isoxazolone derivatives, the yields of desired products (4) are greatly lowered by the formation of several by-products. In fact, in absence of an appropriate arylaldehyde the direct reaction with the diamine gives rise to the partial hydrolysis of (1) and subsequent different reaction pathways. Among these, the formation of the diazepinone (7)[9] occurs to a fair extent (~20%).



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5. 5a, mp 250° (lit.§, mp 249-250°); 5b, mp 195°; 5c,mp 169°; 5d, mp 239°; 5e, mp 241°. New compounds gave the expected analytical and spectroscopic data.
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9. Identified by comparison with a specimen prepared by reaction of the isoxazolone (6) or of the ethylbenzoylacetate with (2), according to the known procedure of M. Israel and L.C. Jones (J. Heter. Chem.,735,1969). Mp. 210°(Found: C, 76.90; H, 5.60; N, 11.25. $C_{16}H_{14}N_2O$ requires C, 76,78; H, 5.64; N, 11.19%); $\nu_{C=O}$(Nujol) 1682 cm^{-1}; $\delta(CDCl_3)$ 8.68 (broad, NH) (disappears with D_2O), 8.13-7.93 (m,2H,aromatic), 7.53-6.93 (m,6H, aromatic), 3.54 (s,2H,methylene) and 2.4 (s,3H,Me).

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