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C,C- and C,N-linked Dimers and 4-Arylmethyl derivatives from 4-Arylmethylene pyrazol-5-ones and isoxazol-5-ones with 2-Arylbenzimidazolines.

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Abstract: 2-arylbenzimidazolines (**8**), generated in situ from o-phenylenediamine (**7**) and the appropriate arylaldehydes, by reaction with 4-arylmethylene pyrazol-5-ones (**1**) or isoxazol-5-ones (**2**) produce the 4-arylmethyl derivatives (**3**) or (**4**) and the C,C- (**5**) or the C,N-linked dimers. The reaction was rationalised on the basis of the role of 2-arylbenzimidazoline as a reducing agent and proceeds by a non-chain, free radical process involving one-electron transfer.

Introduction

Some years ago, we reported[1] on an efficient means of selectively reducing the exocyclic double bond of the 4-arylmethyleneisoxazol-5-ones under mild conditions. The reaction occurred thanks to the reducing ability exhibited by 2-arylbenzimidazoline generated in situ from *o*-phenylenediamine and the appropriate arylaldehyde. Prior to this, there had been one paper on the use of 2-phenylbenzimidazoline for the selective reduction of C-C double bonds conjugated with strong electron-withdrawing groups (CN, NO_2),[2] but not under our efficient reaction conditions.

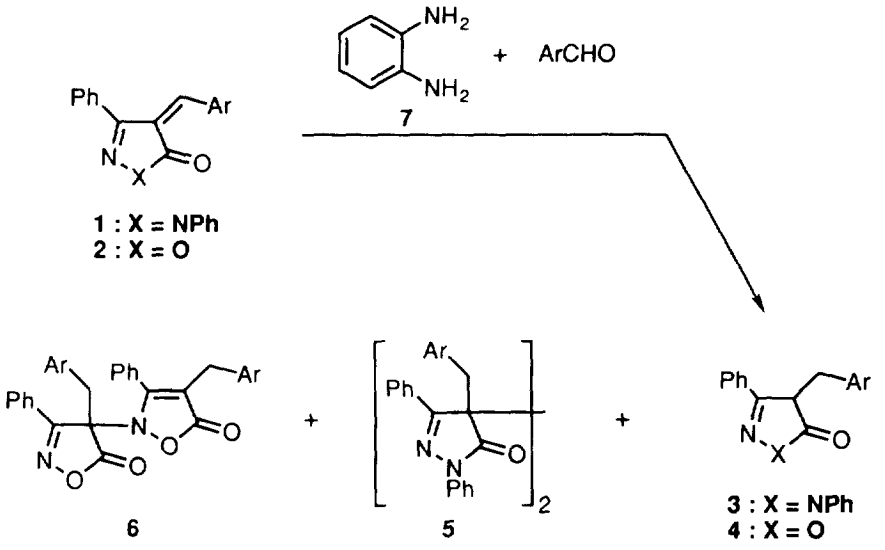
Subsequently the general applicability of the improved method was studied and on the basis of stereochemical and electronic observations a heterolytic or a polar one-step cyclic process was deemed to explain the reduction mechanism of electron-deficient olefins by 2-phenylbenzimidazoline.[3]

More recently, in the course of our studies we have observed the formation of C,C'-linked dimers in the reaction of arylmethylenepyrazol-5-ones with *o*-phenylenediamine and arylaldehyde.[4] The unexpected isolation of coupling products suggested the possible occurrence of a radical pathway for this type of reaction.

The object of the present investigation, therefore, has been to examine in detail the reduction of 4-arylmethylene pyrazol-5-ones **1** and isoxazol-5-ones **2** with 2-arylbenzimidazoline **8** generated in situ with a view to studying the nature of products formed and to determining whether a radical process is actually involved in these reactions.

Results and Discussion

The reactions of 4-arylmethylene pyrazol-5-ones **1** or isoxazol-5-ones **2** (Scheme I) with equimolar amounts of 1,2-phenylenediamine **7** and with arylaldehydes were carried out in refluxing ethanol. Arylaldehyde was added in excess and its aryl group was identical to the 4-substituted substrate **1** or **2**.[5]



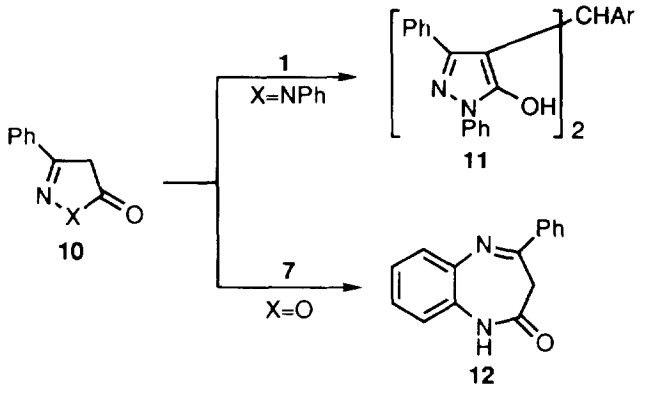
Scheme I

The use of different procedures can favour alternative reaction pathways with a consequent lowering of the yields of the reduced products. Indeed, to quote an example, the absence of a slight excess of arylaldehyde results in partial splitting of 4-arylmethylene substrates accompained by release of the corresponding azolin-5-one **10** and subsequent undesired formation of bis-derivatives[6] **11** in the case of pyrazol-5-ones **1** and diazepinone **12**[1] in the case of isoxazol-5-ones **2** (Scheme II).

Starting from **1** C,C'-linked bipyrazolones **5** were obtained either as pure products or mixed with the reduced products **3**; from **2** the main products were the corresponding arylmethyl derivatives **4** accompained by small amounts of the C,N'-linked biisoxazolones **6**.

The yields are given in Tables I and II. In all cases, benzimidazoles **9** were obtained almost quantitatively with respect to the starting diamine.[7]

Arylmethyl derivatives **3** and **4** and dimers **5** and **6** were isolated by evaporation of the reaction mixture followed either by crystallization or by column chromatography on silica gel.



Scheme II

Table I. Yields and analytical data of arylmethyl derivatives (**3**) and (**4**)

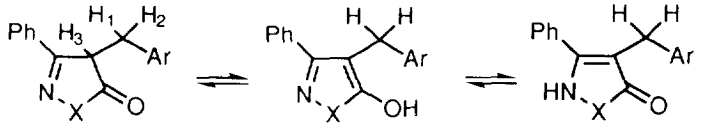
Compd	Ar	mp,°C	yield,%	formula	analysis (calcd/found %) C	H	N
3a	C_6H_5	176	24	$C_{22}H_{18}ON_2$	80.95/80.78	5.56/5.51	8.58/8.68
3b	3-MeC_6H_4	137	65	$C_{23}H_{20}ON_2$	81.15/81.02	5.92/5.87	8.23/8.31
3c[8]	3-$MeOC_6H_4$	128	70	$C_{23}H_{20}O_2N_2$	77.51/77.63	5.66/5.72	7.86/7.95
3d	2-$EtOC_6H_4$	190	68	$C_{24}H_{22}O_2N_2$	77.81/77.68	5.99/5.97	7.56/7.44
4a	C_6H_5	110	90	$C_{16}H_{13}O_2N$	76.47/76.37	5.21/5.18	5.57/5.71
4e	4-MeC_6H_4	111	88	$C_{17}H_{15}O_2N$	76.96/76.86	5.70/5.63	5.28/5.38
4f[9]	2-$MeOC_6H_4$	98	30	$C_{17}H_{15}O_3N$	72.58/72.48	5.37/5.30	4.98/4.81
4g	4-$MeOC_6H_4$	110	88	$C_{17}H_{15}O_3N$	72.58/72.43	5.37/5.35	4.98/5.09
4h	2,4,6-$(Me)_3C_6H_2$	149	80	$C_{19}H_{19}O_2N$	77.79/77.88	6.53/6.50	4.77/4.93
4i	2,4,6-$(MeO)_3C_6H_2$	147	80	$C_{19}H_{19}O_5N$	66.85/66.97	5.61/5.67	4.10/4.34

Table II. Yields and analytical data of dimers (**5**) and (**6**)

Compd	Ar	mp,°C	yield,%	formula	analysis (calcd/found %) C	H	N
5a	C_6H_5	218	56	$C_{44}H_{34}O_2N_4$	81.21/81.40	5.27/5.29	8.61/8.76
5b	3-MeC_6H_4	204	18	$C_{46}H_{38}O_2N_4$	81.39/81.25	5.64/5.59	8.25/8.40
5d	2-$EtOC_6H_4$	173	16	$C_{48}H_{42}O_4N_4$	78.02/78.14	5.73/5.78	7.58/7.72
5e	4-MeC_6H_4	233	76	$C_{46}H_{38}O_2N_4$	81.39/81.22	5.64/5.62	8.25/8.39
5f	2-$MeOC_6H_4$	209	75	$C_{46}H_{38}O_4N_4$	77.72/77.82	5.39/5.44	7.88/7.99
5h	2,4,6-$(Me)_3C_6H_2$	175	70	$C_{50}H_{46}O_2N_4$	81.71/81.59	6.31/6.27	7.62/7.51
5g	4-$MeOC_6H_4$	214	83	$C_{46}H_{38}O_4N_4$	77.72/77.60	5.39/5.37	7.88/7.74
5l	3-ClC_6H_4	212	68	$C_{44}H_{32}Cl_2O_2N_4$	73.43/73.58	4.48/4.50	7.78/7.91
5m	4-ClC_6H_4	221	72	$C_{44}H_{32}Cl_2O_2N_4$	73.43/73.29	4.48/4.42	7.78/7.63
6a	C_6H_5	167	3	$C_{32}H_{24}O_4N_2$	76.78/76.95	4.83/4.85	5.60/5.78
6f	2-$MeOC_6H_4$	125	15	$C_{34}H_{28}O_6N_2$	72.84/72.71	5.03/5.00	5.00/5.18

The structures **3** were assigned on the basis of elemental analyses and spectral data, and confirmed by comparison of their ^{1}H NMR and IR spectra with those of an authentic specimen of 4-benzyl-1,3-diphenylpyrazol-5-one which was synthesized by the reported route[10] and was found to be identical to our product **3a**. The structures **4** were determined by analogy with *ref.* 1.

It is well known that the isoxazol-5-ones and the pyrazol-5-ones can exist in three tautomeric forms, designated CH, NH and OH.[11]



CH form OH form NH form

From ^{1}H NMR and IR data our 3,4-disubstituted compounds **3** and **4** exist predominantly in CH form in chloroform solution, while their NH and OH forms are more common in polar solvents and in the solid state.

In particular, in chloroform (see Table III) pyrazolones **3** and isoxazolones **4** exhibit an ir carbonyl absorption band at approximately 1710 and 1800 cm^{-1}, respectively, and nmr signals corresponding to a coupling of the H-atom at position-4 of the ring with benzylic protons. When the ortho position of the Ar is substituted, the latter are not equivalent and result in abx system.

Table III. Selected spectral data and tautomeric composition of arylmethyl derivatives (**3**) and (**4**) in chloroform

Compd	CH form							NH form		%CH	%NH
	IR[a]	^{1}HNMR[b]						IR[a]	^{1}HNMR[b]		
		H_1	H_2	H_3	$J_{1,2}$	$J_{1,3}$	$J_{2,3}$		CH_2Ar		
3a	1712	3.29	3.48	4.08	-13.6	5.3	4.8	1661	3.87	93	7
3b	1714	3.25	3.39	4.01	-14.1	5.1	5.6	1667	3.81	90	10
3c	1712	3.30	3.43	4.06	-13.6	6.8	2.9	1659	3.87	90	10
3d	1714	2.99	3.36	4.08	-13.4	5.3	8.9	1665	3.85	90	10
4a	1796	3.30	3.30	4.11		5.0	5.0	1738	3.75	70	30
4e	1799	3.24	3.24	4.15		5.4	5.4	1734	3.70	70	30
4f	1798	3.11	3.32	4.05	-13.7	6.9	8.2	1731	3.70	70	30
4g	1802	4.07	4.07	3.27		5.0	5.0	1732	3.70	70	30
4h	1789	3.09	3.27	3.94	-14.4	6.5	10.0	1735	3.68	90	10
4i	1796	3.09	3.30	4.03	-13.7	6.9	8.2			100	—

[a] $CHCl_3$, $\nu_{C=O}$(cm^{-1}). [b] $CDCl_3$, ppm; J, Hz.

In dimethylsulfoxide, CH form is not observed. Ir spectra present an carbonyl absorption band around 1650 and 1680 cm^{-1}, respectively, and nmr spectra a singlet methylene signal around 3.8δ for both derivatives **3** e **4**.

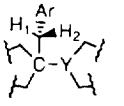
The solid state ir spectra (KBr disk) lack the above carbonyl absorptions but show intermolecular hydrogen-bonded associations making both designations as OH or NH forms equivalent.[11]

These results are consistent with reports in literature.

Dimer structures **5** and **6**, established from analytical and spectroscopic (Table IV) data, were confirmed by independent synthesis from corresponding arylmethylderivatives upon oxidation.[12]

In all studied cases, dimers **5** were obtained in the racemic form; this assignment of stereochemistry was made by X-ray crystallography.[13]

Table IV. Spectral data of dimers (**5**) and (**6**)

Compd	IR[a]	^{1}H NMR[b]				
		H_1(d)	H_2(d)	J,Hz	others	
5a	1705	3.99	4.93	13.2	6.93-7.89(m,15)	
5b	1706	3.86	4.85	14.4	2.06(s,3);6.66-7.90(m,14)	
5d	1711	4.22	5.03	15.0	1.15(t,3);3.90 (q,2,);6.35-7.81(m,14)	Y=C(5), N(6)
5e	1704	3.86	4.82	13.8	2.10(s,3);6.72-7.73(m,14)	
5f	1707	3.98	4.96	14.4	3.23(s,3);6.46-7.88(m,14)	
5h	1715	4.31	4.73	15.0	2.10(s,3);2.39(s,6);6.56-7.83(m,12)	
5g	1706	3.82	4.75	13.8	3.55(s,3);6.42-7.84(m,14)	
5i	1700	3.84	4.81	13.8	6.95-7.88(m,14)	
5m	1695	3.83	4.80	13.8	7.03-7.91(m,14)	
6a	1794 and 1756	3.10	3.33	12.0	3.56(s,2);6.52-8.12(m,20)	
6f	1806 and 1758	3.33	3.56	12.0	3.58(s,2);3.23(s,3);3.62(s,3);6.50-7.96(m,18)	

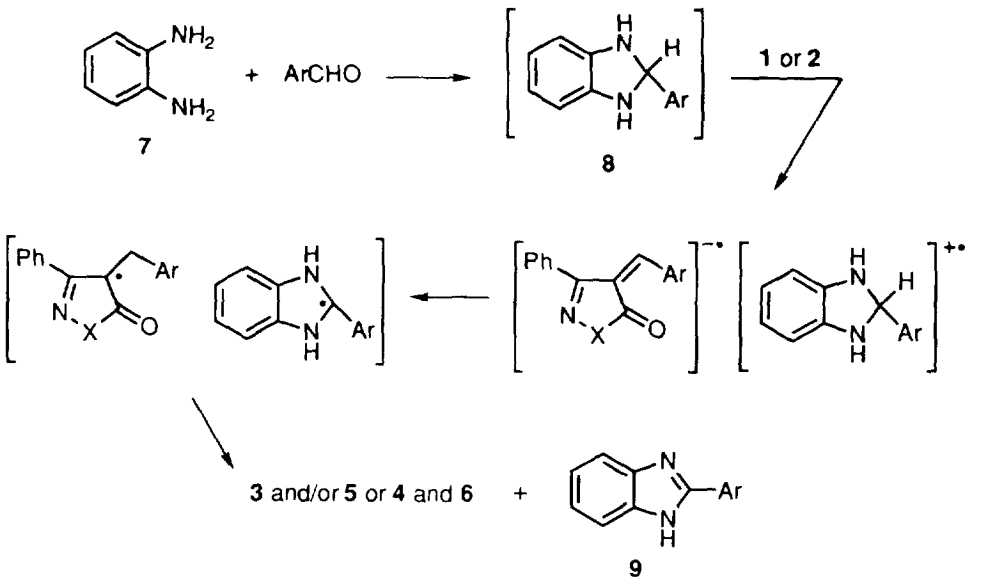
[a] KBr ,$\nu_{C=O}$(cm^{-1}). [b] $CDCl_3$,ppm; J,Hz; Multiplicity and signal intensity(H) indicated by values in parentheses.

The action of 2-arylbenzimidazolines **8** seems to be strongly dependent upon the substrates utilised: olefins conjugated with electron-withdrawing groups each give one product with high yields of the respective saturated derivatives. However, the reaction is negatively influenced by a weakening of the electron-withdrawing power and steric hindrance of the substituents, thus, for example, diethyl benzylidenemalonate doesn't undergo any reaction.[3]

In the cases studied by us, that is the 4-arylmethylene pyrazol-5-ones **1** and isoxazol-5-ones **2**, high yields of the corresponding reduced products were obtained regardless of the steric hindrance of Ar and of the nature of its substituents. As further proof 3-phenyl-4-diphenylmethyleneisoxazol-5-one with 1,2-phenylenediamine and arylaldehyde, were tested under our reaction conditions. The corresponding 4-diphenylmethyl derivate was obtained with a yield of 92%

These results together with evidence that dimers **5** and **6** have never been found in analogous reductions such as, for example, with cyclohexene and 4-arylmethylene pyrazol-5-ones [14] or with $NaBH_4$ and 4-arylmethylene isoxazol-5-ones,[15] nor obtained under our reaction conditions from corresponding preformed 4-arylmethyl derivatives, have unequivocally pointed towards a reaction mechanism involving radicals.

This is perfectly plausible even when the well-known stability of pyrazolinyl radicals is taken into account.[16] Considering these facts and comparing them with the consistently analogous reduction reaction of the α-nitro sulfones with 1,3-dimethyl-2-phenylbenzimidazoline,[17] the course of the reaction may be as proposed in Scheme III. The initiation of the process occurs via single electron transfer, with the formation of an anion radical; this undergoes the transfer of a proton from the benzimidazoline ion radical, rapidly evolving reaction products.



Scheme III

Experimental

M.p.s were determined with Reichert-Kofler hot-stage microscope apparatus and are uncorrected. IR spectra were performed on a Perkin Elmer 682 spectrometer and microanalyses on a Carlo Erba EA 1102 element analyser. ^{1}H NMR ($CDCl_3$) spectra were recorded on a Bruker 80 Q spectrometer with tetramethylsilane as an internal reference. Column chromatography was performed on Merck silica gel 60. Diamine and arylaldehydes were purchased from Aldrich Chemical Company and were used as received. Benzimidazoles were identified by comparison with authentic samples prepared by a known procedure from diamine and the appropriate arylaldehyde.[7]

Starting materials.

4-Arylmethylene-1,3-diphenylpyrazol-5-ones **1a**, **1b**, **1e**, **1g**, **1h**, **1m** were prepared according to the literature.[18] The other arylidene derivatives were obtained by the previously reported method from the 1,3-diphenylpyrazol-5-one and excess corresponding aromatic aldehydes.

1c: brick-red needles, (79%), mp.117°C from EtOH;

1d: bright-red crystals, (77%), mp.167°C from benzene/EtOH;

1f: orange-red crystals, (70%), mp.133°C from benzene/EtOH;

1l: purple-red needles, (68%), mp.171°C from benzene/ EtOH.

4-Arylmethyleneisoxazol-5-ones **2a**,**2e**,**2f**,**2g**[19] and **2h**[20] were prepared as described in the literature.

The new compound **2i** (light yellow crystals from EtOH, mp.188°C) was obtained by standard procedure from the reaction of 3-phenylisoxazol-5-one (0.03mol) and the 2,4,6-trimethoxybenzaldehyde (0.035 mol) in refluxing EtOH.

*Reaction of 4-arylmethylene-1,3-diphenylpyrazol-5-ones **1** with Benzimidazoline **8** generated in situ.*

A solution of diamine (4.0 mmoles) in EtOH was added dropwise over 20 min. to a mixture of **1** (4.0 mmoles) and of the appropriate aromatic aldehyde (5.5 mmoles) in EtOH abs (50 ml) under reflux. Stirring was continued for a further 1 hour and then the reaction mixture was evaporated to give an oil residue which was neutralized with HCl 10% (30 ml). The acidic aqueous suspension was then extracted with ether (3x50ml) and the combined ether extracts were washed with water (75 ml) and dried on sodium sulfate. Filtration, followed by evaporation of the filtrate solvent gave an oil which was crystallized from ethanol or chromatographed on a silica gel column (with chloroform as the eluting solvent) to yield the arylmethyl derivatives **3** and/or the dimeric products **5**. The acidic solution was made alkaline with sodium hydroxide (10%) to give benzimidazoles **9**.

*Reaction of 4-arylmethylene-3-phenylisoxazol-5-ones **2** with Benzimidazoline **8** generated in situ.*

In accordance with the above method described for the reaction of **1**, the reduced products **4** were obtained. In cases **a** and **f**, separation of the reaction products by silica gel chromatography also gave the dimers **6**, but yields were very poor .

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