CONJUGATE ADDITION VS. VINYLIC SUBSTITUTION IN PALLADIUM-CATALYSED REACTION

OF ARYL HALIDES WITH β-SUBSTITUTED-α,β-ENONES AND -ENALS

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Abstract – The reaction of β-substituted- α,β-enones and -enals with
aryl halides in the presence of a palladium catalyst has been
investigated. The outcome of the reaction was found to be greatly
dependent on the nature of the added base. Tertiary amines tend to
favour the formation of conjugate addition-type products while sodium
bicarbonate or sodium acetate that of vinylic substitution products.
Usually, the use of sodium acetate produced results comparable or
better than those obtained with sodium bicarbonate. Furthermore, in
the reaction of aryl halides containing strongly electron-
-withdrawing groups, sodium acetate afforded a dramatic increase in
the yield of vinylic substitution products.

Introduction

It is well known that olefinic systems react with σ-bonded carbon(sp^2)-palladium
complexes to give unstable σ-alkylpalladium species which undergo a rapid, spontaneous
syn-β-elimination of HPdX to form vinylic substitution products.[1] To our knowledge,
however, this reaction has not been extended to β-substituted-α,β-enones and -enals (1). In
our hands, indeed, a variety of β-substituted-α,β-enones and -enals failed to give vinylic
substitution products when reacted with aryl halides, palladium catalyst and tertiary
amines. Poor to moderate yields of conjugate addition-type products were instead obtained
(depending on the nature of the aryl halide). Some representative results are summarized in
the Table 1. This failure can be accounted for by the observations we reported previously[2]
on the decomposition in the presence of tertiary amines of the σ-alkylpalladium
intermediates derived from acyclic α,β-unsaturated carbonyl compounds. The competition

between C_α-Pd bond breaking followed by formation of the C_α-H bond (conjugate addition path; Scheme I,a) and syn-β-elimination of HPdX (vinylic substitution path; Scheme I,b) has been rationalyzed mainly in terms of steric effects related to the nature of the substituents on the β-carbon, electronic effects related to the electron-withdrawing power of the carbonyl group, and basic reaction medium.

According to the pathway a, the palladium atom leaves the organic framework as a Pd(II) species while Pd(0) is necessary to maintain the catalytic cycle. Therefore, unless an efficient reducing system is used (for example trialkylammonium formate),[2,3] the reaction will stop quickly in the presence of catalytic amounts of palladium after production of variable amounts of conjugate addition type derivatives (3) (from traces to poor yield) and vinylic substitution derivatives (4) (minor products). As suggested previously [2] and confirmed now (Table 1), tertiary amines are able to reduce σ-alkyl palladium intermediates to give conjugate addition-type products to some extent. However, their efficiency with acyclic α,β-unsaturated carbonyl compounds is not very high. Recently, the use of triethylamine as the reducing system in the palladium-catalysed Michael arylation of cyclic α,β-unsaturated lactones has been reported.[4]
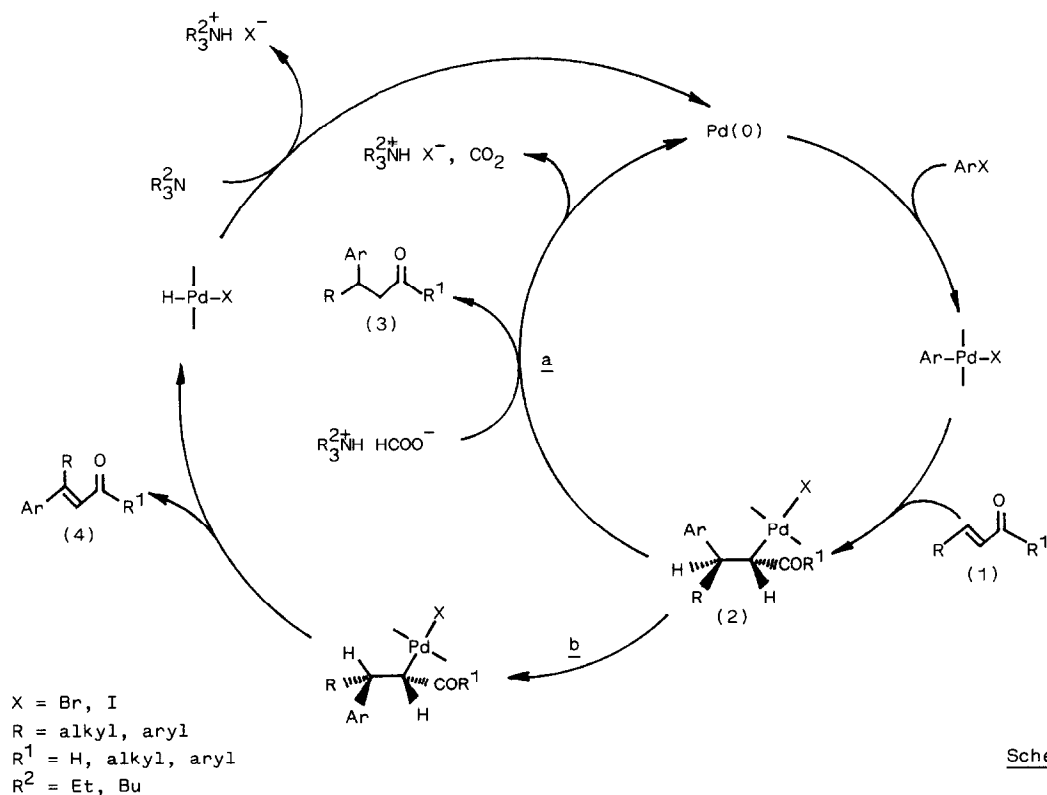

X = Br, I
R = alkyl, aryl
R^1 = H, alkyl, aryl
R^2 = Et, Bu

Scheme I

Table 1 – The Palladium–Catalysed Reaction of Benzalacetone with Aryl Halides in the
Presence of Tributylamine.[a]

Aryl halide	Pd–catalyst	Benzalacetone recovered (% yield)[b]	Conjugate addition type product (% yield)[b]	Vinylic substitution product (% yield)[b]
PhI	Pd(OAc)$_2$(PPh$_3$)$_2$	74	14	--
4–MeO–C$_6$H$_4$–I	Pd(OAc)$_2$(PPh$_3$)$_2$	47	34	7[c]
4–MeO–C$_6$H$_4$–I	Pd(OAc)$_2$	40	22	5[c]
4–MeO–C$_6$H$_4$–I	Pd(OAc)$_2$[P(o–Tol)$_3$]$_2$	57	17	15[c]
4–HO–C$_6$H$_4$–I	Pd(OAc)$_2$(PPh$_3$)$_2$	46	40	13[c]
4–MeCO–C$_6$H$_4$–Br	Pd(OAc)$_2$(PPh$_3$)$_2$	84	--	--
4–MeCO–C$_6$H$_4$–Br	Pd(OAc)$_2$[P(o–Tol)$_3$]$_2$	97	--	--

a) Reactions were carried out at 60 °C (6 h) in DMF by using the following molar ratios:
benzalacetone:ArX:n–Bu$_3$N:Pd–catalyst = 1:1.5:2.5:0.03. b) Yields refer to single, non
optimized runs. c) As E/Z mixture.

Since the extension of the vinylic substitution reaction to ß–substituted–α,ß–enones
and –enals would provide a significative widening of the scope of this methodology in
organic synthesis, it seemed to us of interest to expend efforts in seeking methods to
control the reactivity of (2) in order to favour the formation of vinylic substitution
products. The results of this study are reported hereafter.

Discussion

Selecting benzalacetone and phenyl iodide as model systems and after screening
different conditions*, we have succeded to obtain 4,4–diphenyl–3–buten–2–one in 70%
yield by using NaHCO$_3$ as the base and n–Bu$_4$NCl as phase–transfer catalyst as reported by
Jeffery:**[5]

* For example, by reacting benzalacetone with phenyl iodide in the presence of palladium
catalyst, an excess of NaHCO$_3$, and n–Bu$_4$NHSO$_4$ only traces (2–4%) of the vinylic
substitution product were isolated (benzalacetone was recovered in 80 % yield; 8 h, 60 °C)
suggesting a dependence of the reaction course on the nature of the anion of the ammonium
salt. However, the use of LiCl instead of n–Bu$_4$NCl afforded the vinylic substitution
derivative in 11% yield (benzalacetone was recovered in 78 % yield; 8 h, 60 °C) showing
the need for a more lipophilic cation. This result, unsatisfactory from a synthetic point
of view, may be of interest if compared to the almost complete absence of products
observed when the reaction was carried out in the presence of NaHCO$_3$ alone. It merits a
note that n–Bu$_4$NHSO$_4$ was found to be less efficient than n–Bu$_4$NCl in the Pd–catalysed
reaction of phenyl iodide with 3–buten–2–one in the presence of NaHCO$_3$ (benzalacetone was
isolated in 40% and 59% yield, respectively; 3–buten–2–one:PhI = 1:2, DMF, 24 h, 30°C).
** Benzalacetone was recovered in 84% yield and the vinylic substitution product was
obtained only in traces by substituting Pd(OAc)$_2$(PPh$_3$)$_2$ for Pd(OAc)$_2$.
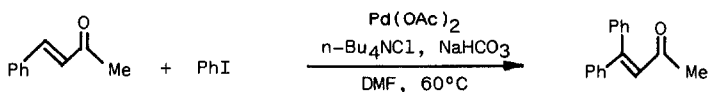
Scheme II

These conditions have been found satisfactory for a variety of aryl iodides and bromides (Table 2, entries h,l,n,q,s). However, we failed to obtain vinylic substitution derivatives in satisfactory yield in the presence of aryl halides containing strongly electron-withdrawing groups (Table 2, entries a,d). In these cases, we observed a dramatic increase in the yield by adding acetic acid to the above reaction mixture (Table 2, entries b,e) or by substituting AcONa for NaHCO$_3$ (Table 2, entry c). The presence of the acetate anion was found to cause an increase of the yield with other functional groups as well (Table 2, entries i,m,u).

Interestingly the acetate anion increased the yield of the reaction even in the absence of n-Bu$_4$NCl. The reaction of benzalacetone with phenyl iodide and AcONa under usual conditions without n-Bu$_4$NCl produced 4,4-diphenyl-3-buten-2-one in 20% yield (benzalacetone was recovered in 68% yield), a result significantly better than that obtained in the presence of tributylamine (Table 1) or NaHCO$_3$ (benzalacetone was in this case recovered unchanged). The conjugate addition type product was formed only in traces.

It is noteworthy that, when benzalacetone was reacted with phenyl iodide in the presence of acetic acid by using a tertiary amine as the base (Table 3, entries a,d,g,l), the conjugate addition-type product was always found to be the major one (results very similar to those obtained with AcOH were also obtained with CF$_3$COOH – Table 3, entries b,e,f,h,i,m – or MeSO$_3$H – Table 3, entry c). At least in this reaction, the combination of tertiary amines with AcOH, CF$_3$COOH or MeSO$_3$H allows reduction of palladium species to occur with an efficiency comparable to that observed with tertiary amines and HCOOH.

56-85%
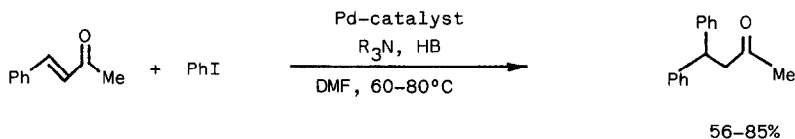
R = Et, n-Bu;
BH = AcOH, CF$_3$COOH, MeSO$_3$H

Scheme III

The question thus arises on how amines, acids and NaHCO$_3$ or AcONa can affect the reactivity of σ-alkylpalladium intermediates (2) and control the balance between conjugate addition and vinylic substitution.

Table 2 – Vinylic Substitution Derivatives Obtained in the Palladium-Catalysed Reaction of Aryl Halides and Benzalacetone.[a]

Entry	Aryl halide	Reaction conditions	Time (h)	Vinylic substitution product (4) (% yield)[b,c]	E/Z relative percentages[d]
a	4-MeCO-C_6H_4-Br	A[e]	6	15 (70)	97:3
b	" "	B[e]	6	84 (--)	98:2
c	" "	C[e]	6	87 (10)	97:3
d	4-OHC-C_6H_4-Br	A[e]	24	-- (--)	--
e	" "	B[e]	24	64 (25)	96:4
f	4-MeOCO-C_6H_4-I	A[f]	24	39 (58)	91:9
g	" "	B[f]	24	42 (56)	94:6
h	3-MeCO-C_6H_4-Br	A[e]	6	52 (37)	91:9
i	" "	B[e]	4	74 (12)	97:3
l	4-MeCONH-C_6H_4-I	A[f]	4.5	64 (30)	98:2
m	" "	C[f]	3.5	78 (18)	98:2
n	PhI	A[f]	8	73 (21)	--
o	"	B[f]	8	70 (23)	--
p	"	C[f]	8	74 (21)	--
q	4-MeO-C_6H_4-I	A[f]	3.5	82 (13)	82:18
r	" "	C[f]	3.5	84 (12)	85:15
s	4-HO-C_6H_4-I	A[f]	3	96 (--)	56:44
t	3-MeOCO-C_6H_4-I	A[f]	7	36 (56)	98:2
u	" "	B[f]	8	47 (48)	98:2

a) Reactions were carried out by using the following molar ratios:
   A = benzalacetone:ArX:n-Bu_4NCl:Pd(OAc)$_2$:NaHCO$_3$ = 1:1.5:1:0.03:4;
   B = benzalacetone:ArX:n-Bu_4NCl:Pd(OAc)$_2$:NaHCO$_3$:AcOH = 1:1.5:1::0.03:4:1.7;
   C = benzalacetone:ArX:n-Bu_4NCl:Pd(OAc)$_2$:AcONa = 1:1.5:1:0.03:1.7.
b) Yields refer to single non optimized runs, and are given for pure isolated products.
c) Figures in parentheses refer to the recovered starting material. d)Relative percentages were determined by ^{1}H-NMR analysis of worked-up reaction mixtures. e) 80°C. f) 60°C.

A reasonable explanation may be based on the assumption that in the presence of tertiary amines coordination of the amine to the palladium[6] can produce a late pentacoordinated transition state[7] with a high anionic character on the C_α. This behaviour strongly favours the formation of conjugate addition-type products and can be facilitated by the ability of the carbonyl group to stabilize a negative charge on the C_α. The acid could be involved in the decomposition of (2) as the proton source for the protonation of the anionic moiety of this loose σ-alkylpalladium species.
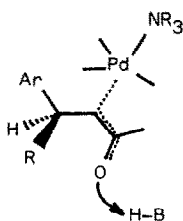
Table 3 — Catalysts, Tertiary Amines, and Acids, in the Reaction of Benzalacetone with Phenyl Iodide.[a]

Entry	Base	Acid	Pd catalyst (5 mol %)	Time (h)	Total yield, %	Products, yield %		
						Starting material	Conjugate addition	Vinylic substitution
a	Et_3N	AcOH	Pd/C 5%	4	87	10.3	69	20.7
b	Et_3N	CF_3COOH	Pd/C 5%	4	89	24.7	67.4	7.9
c	Et_3N	$MeSO_3H$	Pd/C 5%	4	87	16.7	70.7	12.6
d	$n-Bu_3N$	AcOH	Pd/C 5%	4	65	10.8	86.2	3
e	$n-Bu_3N$	CF_3COOH	Pd/C 5%	4	65	3.1	90.8	6.1
f[c]	$n-Bu_3N$	CF_3COOH	Pd/C 5%	4	69	5.8	94.2	–
g[c,d]	$n-Bu_3N$	AcOH	Pd/C 5%	15	80	8.7	91.3	–
h[c,d]	$n-Bu_3N$	CF_3COOH	Pd/C 5%	15	79	7.6	92.4	–
i[c,e]	$n-Bu_3N$	CF_3COOH	$Pd(OAc)_2(PPh_3)_2$	7	90	11.1	88.9	–
l[c,e]	$n-Bu_3N$	AcOH	$Pd(OAc)_2(PPh_3)_2$[f]	7	76	–	100	–
m[c,e]	$n-Bu_3N$	CF_3COOH	$Pd(OAc)_2(PPh_3)_2$[f]	7	85	–	100	–

a) Unless otherwise noted, reactions were carried out with 3.42 mmol of benzalacetone, 8.16 mmol of phenyl iodide, 15.23 mmol of tertiary amine, 8.98 mmol of acid, 0.017 mmol of catalyst in DMF (1ml) at 80°C under an argon atmosphere. b) GLC yield. c) In the presence of 0.34 mmol of $n-Bu_4NI$. d) At 60°C. e) At 70°C. f) 10 mol %.

The protonation allows the C_α-Pd bond breaking to occur faster than the sequence: rotation around the C_α-C_β bond/syn-β-hydridopalladium elimination. Protonation of intermediates (2) has already been suggested to allow the formation of conjugate addition-type products in the palladium catalysed reaction of arylmercury[8,9] and aryltin[8] compounds with α,β-enones.

When $NaHCO_3$ and AcONa are substituted for tertiary amines, the β-elimination of HPdX could be favoured by a reduced extent of C_α-Pd bond cleavage in the transition state and/or

a minor availability of protons from the medium*. The tendency to give the ß-elimination of

HPdX in the presence of these bases is confirmed by the result obtained in the reaction of

benzalacetone with phenyl iodide, Pd(OAc)$_2$, HCOOH, n-Bu$_4$NCl and NaHCO$_3$ or AcONa. Under these

conditions a mixture of the conjugate addition-type derivative (22-24% yield) and vinylic

substitution derivative (26-29% yield) was obtained. The starting material was recovered in

39-40% yield. Under closely related conditions, but using Et$_3$N as the base, the

conjugate-addition type derivative was isolated in 71% yield and the vinylic substitution

product was observed only in traces.[2]

The hypothesis that NaHCO$_3$ and AcONa could promote a less precedented[11] anti-

-ß-elimination of HPdX was ruled out on the ground of the observed stereochemistry of the

main vinylic substitution derivatives. In fact, ^{1}H-NMR and X-ray analyses revealed main

vinylic substitution products to derive from syn-addition of arylpalladium species to the

carbon-carbon double bond and syn-ß-elimination of HPdX.

^{1}H-NMR spectra of E/Z mixtures of vinylic substitution products in the presence of

variable amounts of the paramagnetic shift reagents Eu(fod)$_3$ or Eu(dpm)$_3$ in the range of

0.2-1.0 shift reagent/substrate molar ratio showed that the olefinic proton was invariably

shifted the greater in all the major isomers, independently of the donor power of the group

on the aromatic ring. From Dreiding models, olefinic protons were found to be closer to the

coordination site on the aromatic ring in E-isomers, irrespective of the conformation

adopted by the molecule; thus E-configuration to the major isomers (products from

syn-addition/syn-ß-elimination) was conceivably assigned. As an example, the results

obtained with the E/Z mixture of (4d) are summarized in the Table 4.

Table 4 — δ Values for the E/Z Mixture of (4d) in the Presence of Variable
Amounts of Eu(dpm)$_3$

| Eu(dpm)$_3$/substrate ratio	δ Values (ppm; CDCl$_3$/TMS)		Δδ = δ$_E$−δ$_Z$
	E isomer	Z isomer	
0.0	6.65	6.73	−0.08
0.2	6.73	6.76	−0.03
0.4	10.83	10.83	0.00
0.8	10.63	10.47	0.16

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* The presence of a protic medium, however, does not appear to play a dominant role.
  Decomposition of the σ-alkylpalladium intermediate derived from chalcone and phenyl-
  palladium acetate in acetic acid has been reported to occur through syn-ß-elimination of
 HPdOAc.[10]
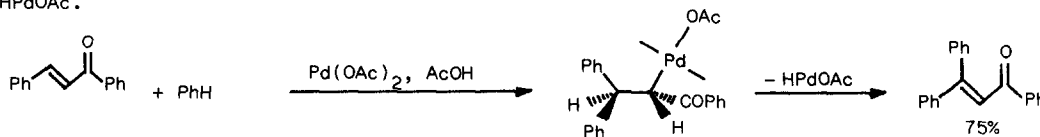
Results of X-ray analyses of compounds (4a) and (41) are reported in the next section.

The isomeric vinylic substitution derivatives (5) were usually obtained in only very low yield. Only in the presence of 4-hydroxy group the formation of a significant amount of (5) was observed (Table 2, entry s), most likely as the result of an E/Z isomerization of the initially formed syn-ß-elimination product, favoured by the free phenolic group. Whatever the real reason of this behaviour may be, substitution of the methyl group for the labile proton (Table 2, entries q,r) affords the vinylic substitution derivative in the usual E/Z ratio.
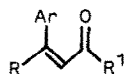
(5)

As concerns the effect of the acetate anion on the reaction course, an explanation based on the formation of a σ-alkylpalladium acetate and its decomposition through basic intramolecular attack of the acetate moiety on the ß-hydrogen is tentatively proposed (Scheme IV, a). Related mechanisms involving a seven-membered cyclic transition state containing palladium have been suggested to account for the regio- and stereochemistry of carbon monoxide induced acetate migration from palladium to an unsaturated carbon ligand in π-allylpalladium complexes[12] and of palladium-catalysed 1,4-functionalyzation of cyclic 1,3-dienes[13] (Scheme IV, b), and for the palladium-catalysed regioselective formate reduction of allyl acetates to terminal alkenes[14] (Scheme IV, c).
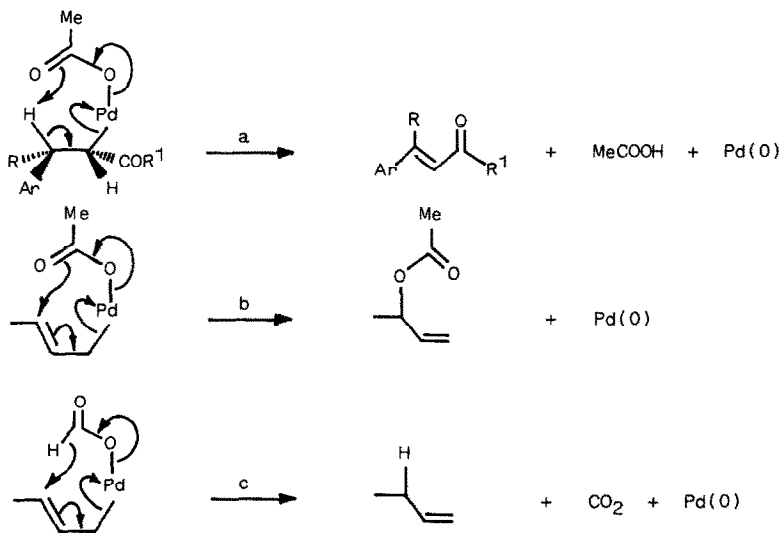
Scheme IV

ß–Hydrogen abstraction by the acetate complexed to the σ–alkylpalladium species is in agreement with both stereochemical results (main products derive from syn–ß–elimination) and electronic effects (greatest effects are observed with aromatic rings containing strongly electron–withdrawing groups; in these cases hydridopalladium elimination is conceivably more difficult). Furthermore, benzalacetone was recovered unchanged when reacted with 4–acetylphenyl bromide in the presence of the less basic trifluoroacetate anion (compare entries b and c, Table 2).

In the Table 5 the results obtained using either NaHCO$_3$ or AcONa as the bases and various ß–substituted–α,ß–enones or –enals and aryl halides as susbtrates are summarized. It is worth noting that with α,ß–unsaturated carbonyl compounds bearing an alkyl group on the ß–carbon atom essentially the same results were obtained with and without acetate even with aryl halides containing electron–withdrawing groups (Table 5, entries m, n). In these cases main products were found to be the E/Z mixtures of vinylic derivatives (6), most likely arising from readdition–elimination of HPdX species:

R = Et; n–Pr

Ar = 4–MeCO–C$_6$H$_4$

Scheme V

In conclusion, the results reported in this paper show that the reactivity of σ–alkyl-palladium intermediates derived from the reaction of ß–substituted–α,ß–enones and –enals with aryl halides can be effectively controlled by the nature of the base thus providing a simple and efficient tool to select different synthetic pathways for the same starting materials through subtle changes in the reaction medium.

The Crystal Structure

The stereochemistry of the vinylic substitution products (4a) and (4l) has been unambiguously established by X-ray crystal structure analysis. Figure 1 shows the molecular structures of these compounds exhibiting the E configuration of the vinylic double bond. The atomic coordinates and thermal parameters of the non-hydrogen atoms of the two structures are listed in Table 6.

Table 5 – Vinylic Substitution Derivatives Obtained in the Palladium–Catalysed Reaction of Aryl Halides and ß–Substituted–α,ß–Enones and Enals.[a]

Entry	α,ß–Unsaturated carbonyl compounds	Aryl halide	Reaction conditions	Vinylic substitution product (4) (% yield)[b,c]	E/Z relative percentages[d]
a	Ph~~CHO (structure)	PhI	A[e]	43 (55)	– –
b	"	PhI	C[e]	57 (39)	– –
c	"	4–HO–C6H4–I	A[e]	67 (30)	63:37
d	"	4–MeCONH–C6H4–I	A[e]	84 (14)	83:17
e	"	4–MeCO–C6H4–Br	C[f]	46 (38)	87:13
f	Ph~~CO–Et (structure)	PhI	A[e]	81	– –
g	Ph~~CO–Ph (structure)	3–HOCH2–C6H4–I	A[e]	60 (20)	91:9
h	Ph~~CO–C4H9 (structure)	4–MeCO–C6H4–Br	A[f]	36 (60)	89:11
i	"	" "	C[f]	66 (30)	99:1
l	(structure) CHO	4–HO–C6H4–I	A[g,e]	74 (20)[h]	59:41
m	(structure) CO	4–MeCO–C6H4–Br	A[g,f]	16 (51)[h]	92:8
n	"	" "	C[g,f]	15 (60)[h]	98:2
o	(structure) CO	4–MeCO–C6H4–Br	C[g,f]	17 (52)[h]	96:4

a) Reactions were carried out (8 h) by using the following molar ratios:
   A = benzalacetone:ArX:n–Bu4NCl:Pd(OAc)2:NaHCO3 = 1:1.5:1:0.03:4;
   C = benzalacetone:ArX:n–Bu4NCl:Pd(OAc)2:AcONa = 1:1.5:1:0.03:1.7.
b) Yields refer to single non optimized runs, and are given for pure isolated products.
c) Unless otherwise stated, figures in parentheses refer to the recovered starting material.
d) Relative percentages were determined by ^{1}H–NMR analysis of worked-up reaction mixtures.
e) 60°C. f) 80°C. g) 24 h. h) Yield of the E/Z mixture of vinylic derivative (6).

The bond distances and the valence angles generally fall within the range of accepted values. Unusual values are only observed in the extreme part of the benzene ring of compound (41), and they can be ascribed to the bad location of the atoms, due to their large thermal factors.

In the solid state, the molecules of the two compounds show a similar arrangement of the aromatic rings and of the vinylic moiety. In compound (4a), the dihedral angles between the planes of the rings A and B and that of the double bond C(4)=C(5) are 59 and 20°. The corresponding values for compound (41) are 58 and 37°. These structural parameters lead to a
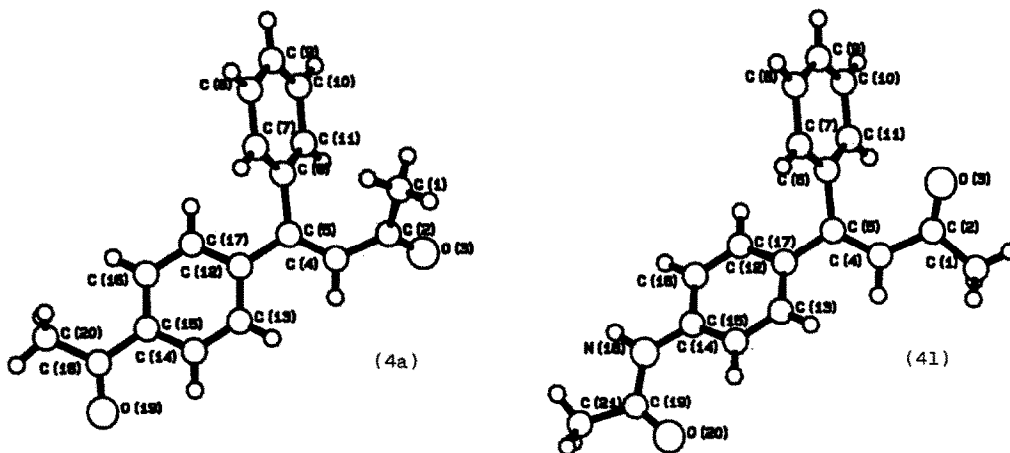
Fig. 1 — Molecular structures of (4a) and (41).

nearly perpendicular orientation of the two aromatic systems, being 79° the angle between their best planes in both the molecules.The groups —COMe and —NHCOMe, substituents of the B ring of the two molecules, are almost coplanar with this ring, being 12 and 15° the angle between their planes in compound (4a) and (41), respectively.

A major difference between the structures is found in the conformation of the —COMe group at C(4) with respect to the rest of the molecule. The carbonyl C(2)=O(3) is anti-periplanar, in (4a), and syn-periplanar, in (41), to the double bond C(4)=C(5). This conformational variation may be attributable to a higher efficiency of the crystal packing, which in both cases is mainly governed by Van der Waals forces. In the crystal of compound (41), molecules related by two-fold screw axes are also linked by intermolecular hydrogen bonds involving N(18) and O(20), with the following geometrical parameters: N(18)....O(20) = 3.05 Å, H(N(18))....O(20) = 2.09 Å, N(18)–H....O(20) = 172.6° and C(19)=O(20)....H(N(18)) = 150.4°.

EXPERIMENTAL

M.ps were determined with a Büchi 510 apparatus and are uncorrected. All starting materials, catalysts and solvents are commercially available and were used without further purification. 4-Acetylaminophenyl iodide, as well as 3-carbomethoxy- and 4-carbomethoxy-phenyl iodides were prepared from commercially available 4-aminophenyl iodide and 3-iodo and 4-iodobenzoic acids according to standard methods. 1-Phenyl-1-penten-3-one was prepared from commercially available 1-penten-3-one and phenyl iodide according to   Jeffery.[5] Reactions were carried out on a 0.62-4.0 mmol scale.

Table 6 - Atomic coordinates and isotropic thermal parameters with their e.s.d.'s in parentheses.

		$\underline{x}$	$\underline{y}$	$\underline{z}$	$B(eq)$[a]
Compound (4a)	C(1)	-0.0905(3)	0.0083(3)	0.1345(3)	6.2(1)
	C(2)	-0.0580(3)	0.0275(2)	0.2729(3)	4.5(1)
	O(3)	-0.1372(2)	0.0134(2)	0.3141(2)	6.4(1)
	C(4)	0.0732(2)	0.0524(2)	0.3635(2)	4.2(1)
	C(5)	0.1581(2)	0.1196(2)	0.3470(2)	3.7(1)
	C(6)	0.1239(2)	0.1942(2)	0.2338(2)	3.6(1)
	C(7)	0.1887(3)	0.1885(2)	0.1561(2)	4.4(1)
	C(8)	0.1561(3)	0.2600(2)	0.0518(2)	4.8(1)
	C(9)	0.0578(3)	0.3366(2)	0.0236(3)	5.1(1)
	C(10)	-0.0070(3)	0.3424(2)	0.0990(3)	5.1(1)
	C(11)	0.0263(3)	0.2724(2)	0.2042(3)	4.5(1)
	C(12)	0.2894(2)	0.1285(2)	0.4467(2)	3.9(1)
	C(13)	0.3425(3)	0.0417(2)	0.5363(2)	4.4(1)
	C(14)	0.4631(3)	0.0510(2)	0.6292(2)	4.6(1)
	C(15)	0.5384(2)	0.1444(2)	0.6368(2)	4.0(1)
	C(16)	0.4876(2)	0.2313(2)	0.5485(2)	4.2(1)
	C(17)	0.3644(2)	0.2231(2)	0.4554(2)	4.2(1)
	C(18)	0.6708(3)	0.1472(2)	0.7369(2)	4.6(1)
	O(19)	0.7038(2)	0.0778(2)	0.8225(2)	6.5(1)
	C(20)	0.7622(3)	0.2332(3)	0.7327(3)	6.7(1)
Compound (4l)	C(1)	0.4023(5)	-0.4406(4)	0.4124(2)	7.6(1)
	C(2)	0.3575(4)	-0.3036(3)	0.3880(2)	5.4(1)
	O(3)	0.2644(4)	-0.2341(3)	0.4199(1)	7.8(1)
	C(4)	0.4279(4)	-0.2626(3)	0.3222(1)	5.4(1)
	C(5)	0.4245(3)	-0.1402(3)	0.2921(1)	4.8(1)
	C(6)	0.3572(4)	-0.0188(3)	0.3250(2)	5.6(1)
	C(7)	0.2340(5)	0.0552(4)	0.2892(2)	7.9(1)
	C(8)	0.1695(6)	0.1719(4)	0.3239(3)	10.4(2)
	C(9)	0.2399(8)	0.2016(4)	0.3914(4)	10.9(2)
	C(10)	0.3605(7)	0.1331(5)	0.4239(3)	10.4(2)
	C(11)	0.4181(5)	0.0218(4)	0.3920(2)	7.5(1)
	C(12)	0.4944(4)	-0.1211(3)	0.2235(1)	4.7(1)
	C(13)	0.4758(4)	-0.2176(3)	0.1710(1)	5.1(1)
	C(14)	0.5406(4)	-0.2005(3)	0.1067(1)	5.0(1)
	C(15)	0.6294(3)	-0.0857(3)	0.0934(1)	4.6(1)
	C(16)	0.6492(4)	0.0119(3)	0.1454(1)	5.4(1)
	C(17)	0.5825(4)	-0.0049(3)	0.2087(1)	5.5(1)
	N(18)	0.6999(3)	-0.0591(2)	0.0294(1)	4.9(1)
	C(19)	0.7288(4)	-0.1474(3)	-0.0225(1)	4.0(1)
	O(20)	0.6946(3)	-0.2668(2)	-0.0199(1)	6.2(1)
	C(21)	0.8091(5)	-0.0873(3)	-0.0832(2)	6.4(1)

a) $B(eq) = (4/3) \Sigma_{ij} \underline{a}_i \underline{a}_j b_{ij}$.

The products were purified by preparative HPLC (Chromatospac Prep 10 from Jobin Yvon equipped with a Prep LC/System 500A - solvent delivery system and refractive index detector - from Waters Ass.) on axially compressed columns packed with silica gel 20-45 μ (Amicon Co.) eluting with n-hexane/AcOEt mixtures.

^{1}H-NMR spectra were recorded with a Varian EM-390 spectrometer (TMS internal standard). IR spectra were recorded with a Nicolet 5DX FT/IR spectrometer.

All of the isolated products gave satisfactory microanalyses.

General procedures of reaction of α,β-unsaturated carbonyl compounds and aryl halides

Procedure A - This is exemplified by the reaction of 1-phenyl-1-penten-3-one with phenyl iodide (Table 5, entry f). A solution of 1-phenyl-1-penten-3-one (0.307 g, 1.92 mmol), phenyl iodide (0.587 g, 2.88 mmol), n-Bu$_4$NCl (0.534 g, 1.92 mmol), NaHCO$_3$ (0.645 g, 7.68 mmol) in DMF (4 ml) was added with stirring to a solution of Pd(OAc)$_2$ (0.0129 g, 0.0576 mmol) in DMF (1 ml). The mixture was purged with nitrogen and stirred at 60 °C under a nitrogen atmosphere for 8 h; diethyl ether and water were added, the organic layer was separated, washed with water, dried (MgSO$_4$) and concentrated at reduced pressure. The residue was purified by preparative HPLC eluting with a 95/5 n-hexane/AcOEt mixture to give compound (4f) (0.453 g, 81% yield).

Procedure B - This is exemplified by the reaction of benzalacetone with 4-acetylphenyl bromide (Table 2, entry b). A solution of benzalacetone (0.250 g, 1.70 mmol), 4-acetylphenyl bromide (0.517 g, 2.60 mmol), n-Bu$_4$NCl (0.472 g, 1.70 mmol), NaHCO$_3$ (0.544 g, 6.80 mmol), AcOH (0.166 ml, 2.90 mmol) in DMF (3 ml) was added with stirring to a solution of Pd(OAc)$_2$ (0.012 g, 0.051 mmol) in DMF (1 ml). The mixture was purged with nitrogen and stirred at 80 °C under a nitrogen atmosphere for 6 h. Work up as before afforded a residue which was purified by preparative HPLC eluting with a 80/20 n-hexane/AcOEt mixture to give compound (4b) (0.377 g, 84% yield).

Procedure C - This is exemplified by the reaction of benzalacetone with 4-acetylaminophenyl iodide (Table 2, entry m). A solution of benzalacetone (0.250 g, 1.70 mmol), 4-acetylaminophenyl iodide (0.678 g, 2.60 mmol), n-Bu$_4$NCl (0.472 g, 1.70 mmol), AcONa (0.238 g, 2.90 mmol) in DMF (3 ml) was added with stirring to a solution of Pd(OAc)$_2$ (0.012 g, 0.051 mmol) in DMF (1 ml). The mixture was purged with nitrogen and stirred at 60 °C under a nitrogen atmosphere for 3.5 h. Work up as before afforded a residue which was purified by preparative HPLC eluting with a 50/50 n-hexane/AcOEt mixture to give compound (4m) (0.371 g, 78% yield).

Reaction of 3-octen-2-one and 4-acetylphenyl bromide (Table 5, entry m)

A solution of 3-octen-2-one (0.250 g, 1.98 mmol), 4-acetylphenyl bromide (0.591 g, 2.97 mmol), n-Bu$_4$NCl (0.550 g, 1.98 mmol), NaHCO$_3$ (0.665 g, 7.92 mmol) in DMF (1 ml) was added with stirring to a solution of Pd(OAc)$_2$ (0.0133 g, 0.059 mmol) in DMF (0.5 ml). The mixture was purged with nitrogen and stirred at 80 °C under a nitrogen atmosphere for 24 h; diethyl ether and water were added, the organic layer was separated, washed with water, dried (MgSO$_4$) and concentrated at reduced pressure. The residue was purified by preparative HPLC eluting with a 75/25 n-hexane/AcOEt mixture to give compound (4m) (0.076 g, 16% yield) and an E/Z mixture of compound (6m) which was not further purified (0.246 g, 51 %; mp = oil; IR (liquid film) 1712; 1680; 1606; 1269; 958; 843 cm^{-1}; ^{1}H-NMR: δ 8.12-7.88 (m, 2H); 7.58-7.25 (m, 2H); 6.13 (t, J = 6.7 Hz, 0.6 H); 5.7 (t, J = 6.7 Hz, 0.4 H); 3.65 (s, 1.2 H); 3.47 (s, 0.8 H); 2.55 (s, 3H); 2.38-1.85 (m, 5H); 1.78-1.77 (m, 2H); 1.1-0.73 (m, 3H).

Reaction of benzalacetone with phenyl iodide, formic acid and sodium bicarbonate

A solution of benzalacetone (0.250 g, 1.70 mmol), phenyl iodide (0.530 g, 2.60 mmol), n-Bu$_4$NCl (0.472 g, 1.70 mmol), NaHCO$_3$ (0.571 g, 6.80 mmol) in DMF (4 ml) was added with stirring to a solution of Pd(OAc)$_2$ (0.012 g, 0.051 mmol) in DMF (1 ml). The mixture was purged with nitrogen and formic acid (0.109 ml, 2.90 mmol) was added all at once. The mixture was stirred at 60 °C under a nitrogen atmosphere for 8 h; diethyl ether and water were added, the organic layer was separated, washed with water, dried (MgSO$_4$) and

Table 7 - Characterization of Vinylic Substitution Products (E Isomers) Derived from the Reaction of Benzalacetone with Aryl Halides

Compound (4) Ar	M.p. (°C)	I.R. ν (cm^{-1})	^{1}H-NMR δ (ppm) CDCl$_3$
4-MeCO-C$_6$H$_4$	83-84	1680, 1655, 1606, 843, 777, 703[a]	7.95 (d, J=8.2 Hz, 2H), 7.57-7.16 (m, 7H) 7H) 6.61 (s,1H), 2.56 (s,3H), 1.87 (s,3H)
4-OHC-C$_6$H$_4$	229-230[b]	1696, 1655, 1606, 826, 777, 703[c]	10.07 (s, 1H), 7.88 (d, J = 8.2 Hz, 2H), 7.62-7.15 (m, 7H), 6.65 (s, 1H), 1.90 (s, 3H)
4-MeOCO-C$_6$H$_4$	63-64	1721, 1655, 1606, 1286,859,769,703[a]	7.63-7.07 (m, 9H), 6.62 (s, 1H), 2.28 (s, 3H),1.88 (s, 3H)
3-MeCO-C$_6$H$_4$	222-223[b]	1688, 1655, 1589, 802, 777, 695[c]	8.07-7.81 (m, 2H), 7.61-6.94 (m, 7H), 6.62 (s,1H), 2.53 (s, 3H), 1.88 (s, 3H)
4-MeCONH-C$_6$H$_4$	121-122	3312, 1688, 1663, 1589, 1179, 835, 777, 703[a]	8.47 (bs, 1H), 7.73-7.10 (m, 9H), 6.60 (s, 1H), 2.14 (s, 3H), 1.88 (s, 3H)
Ph	99-100[b]	1688, 1663, 1606, 1589,777,761,703[c]	7.58-7.08 (m, 10H), 6.58 (s, 1H), 1.81 (s, 3H)
4-MeO-C$_6$H$_4$	179-180[b]	1688, 1655, 1589, 1253,835,769,703[c]	7.76-6.78 (m, 9H), 6.62 (s, 1H), 3.82 (s, 3H), 1.86 (s, 3H)
4-HO-C$_6$H$_4$	oil	3410, 835, 777, 761, 695[c]	7.58-6.52 (m, 11H), 1.93 (s, 1.32 H), 1.85 (s, 1.68 H)
3-MeOCO-C$_6$H$_4$	183-184[b]	1729, 1688, 1663, 1606,1294,761,703[c]	8.25-7.92 (m,2H), 7.62-7.12 (m,7H), 6.62 (s, 1H), 3.87 (s, 3H), 1.87 (s, 3H)

a) KBr. b) As the 2,4-dinitrophenylhydrazone. c) Liquid film. d) Isolated and analyzed as E/Z mixture.

concentrated at reduced pressure. The residue was filtered on a short silica gel column eluting with a 80/20 n-hexane/ethyl acetate mixture to give a mixture of vinylic substitution product, conjugate addition-type product, and starting benzalacetone (overall yield 88 %) whose relative percentages (29.5 %, 25 %, 45.5 %, respectively) were determined by ^{1}H-NMR.

Reaction of benzalacetone with phenyl iodide, formic acid and sodium acetate

A solution of benzalacetone (0.250 g, 1.70 mmol), phenyl iodide (0.530 g, 2.60 mmol), n-Bu$_4$NCl (0.472 g, 1.70 mmol), NaHCO$_3$ (0.923 g, 8.55 mmol), AcOH (0.174 g, 2.91 mmol) in DMF (4 ml) was added with stirring to a solution of Pd(OAc)$_2$ (0.012 g, 0.051 mmol) in DMF (1 ml). The mixture was purged with nitrogen and formic acid (0.109 ml, 2.90 mmol) was added all at once. The mixture was stirred at 60 °C under a nitrogen atmosphere for 8 h. Work up as before afforded a mixture of vinylic substitution product, conjugate addition-type product, and starting benzalacetone (overall yield 93 %) whose relative percentages (31 %, 26 %, 43 %, respectively) were determined by ^{1}H-NMR.

Crystal data and crystal structure determinations

Well shaped colourless prismatic crystals of (4a) were grown from dichloromethane/ n-hexane; plate shaped, poor quality, pale yellow crystals of compound (41) were obtained from dichloromethane/n-hexane. The space groups and approximated unit-cell parameters were determined from oscillation and Weissenberg photographs. The intensity data of (4a) were measured with a Syntex P2$_1$ automatic diffractometer equipped with graphite monochromator and Mo-K$_\alpha$ radiation, in θ-2θ scan mode; for compound (41) Cu-K$_\alpha$ radiation was used. The refined unit-cell dimensions were derived by least-squares calculations of the angular settings of

Table 8 – Characterization of Vinylic Substitution Products (E Isomers) Derived from the Reaction of ß–Substituted–α,ß–Enones and –Enals with Aryl Halides

Compound (4)			M.p.	I.R.	^{1}H–NMR
Ar	R	R[1]	(°C)	ν (cm^{-1})	δ (ppm) CDCl$_3$
Ph	Ph	H	191–192[a]	2844,1663,1589, 1122, 769, 695[b]	9.60 (d, J=8.2 Hz, 1H), 7.64–7.18 (m, 10H), 6.62 (d, J = 8.25 Hz, 1H)
4–HO–C$_6$H$_4$	Ph	H	oil[c]	3181,1663,1639, 1606,1286, 835, 777, 744, 703[b,c]	9.60 (d, J=8.2 Hz, 0.63 H), 9.47 (d, J=8.2 Hz, 0.37 H), 7.63–6.50 (m, 11H)[c]
4–MeCONH–C$_6$H$_4$	Ph	H	248–249[a]	3312,1663,1598, 835, 744, 703[b]	9.56 (d,J=8.2 Hz,1H), 8.67 (bs, 1H), 7.82–7.18 (m ,9H), 6.56 (d, J = 8.2 Hz, 1H), 2.16 (s, 3H)
4–MeCO–C$_6$H$_4$	Ph	H	91–93	1680,1655,1598, 835, 761, 695[d]	9.65 (d,J = 9.2 Hz, 1H), 8.02 (d, J = 8.2 Hz,2H), 7.64–7.22 (m,7H), 6.64 (d, J =8.2 Hz, 1H), 2.60 (s, 3H)
Ph	Ph	Et	131–132[a]	1688,1663,1589, 769, 695[b]	7.62–7.12 (m, 10H), 6.62 (s, 1H), 2.25 (q, J =6.7 Hz, 2H), 0.93 (t, J = 6.7 Hz, 3H)
3–HOCH$_2$–C$_6$H$_4$	Ph	Ph	177–178[a]	3443,1655,1598, 1220, 859, 794, 777, 703[b]	8.05–7.82 (m, 2H), 7.62–7.08 (m, 13H), 4.67 (s, 2H), 2.17 (bs, 1H)
4–MeCO–C$_6$H$_4$	Ph	n–C$_5$H$_{11}$	101–102[a]	1688,1606,1269, 826, 777, 703[b]	7.97 (d, J = 8.7Hz,2H), 7.58–7.12 (m,7H), 6.65 (s,1H), 2.56 (s,3H), 2.25 (t, J=6.7 Hz, 2H), 1.72–0.98 (m, 6H), 0.82 (t, J = 6.7 Hz, 3H)
4–HO–C$_6$H$_4$	n–C$_3$H$_7$	H	oil[c]	3443,1663,1605, 1220, 835[b,c]	10.17 (d, J=8.2 Hz, 0.41 H), 9.53 (d, J=8.2 Hz, 0.59 H), 7.48 (d,J= 8.2 Hz,0.82 H), 7.21 (d,J=8.2 Hz, 1.18 H), 6.94 (d, J =8.2 Hz, 2H), 6.36 (d, J = 8.2 Hz,0.59 H), 6.15 (d, J=8.2 Hz,0.41 H), 3.00 (t, J= 7.5 Hz, 0.82 H), 2.57 (t, J = 7.5 Hz, 1.18 H), 1.77–1.32 (m, 2H), 1.05–0.78 (m, 3H)[c]
4–MeCO–C$_6$H$_4$	n–C$_3$H$_7$	Me	196–197[a]	1680,1598,1269, 958, 826[b]	8.05 (d, J=8.2 Hz,2H), 7.64 (d, J = 8.2 Hz, 2H), 6.52 (s, 1H), 3.19–2.90 (m, 2H), 2.6 (s, 3H), 2.28 (s, 3H), 1.57–1.07 (m, 4H), 1.00–0.67 (m, 3 H)
4–MeCO–C$_6$H$_4$	Et	Me	194–195[a]	1680,1598,1269, 958, 826[b]	8.10 (d,J=8.2 Hz,2H), 7.64 (d, J= 8.2 Hz,2H), 6.52 (s,1H), 3.07 (t, J=8.2 Hz,2H), 2.62 (s,3H), 1.68– –1.18 (m, 2H), 0.92 (d, J=8.2 Hz, 3H)

a) As the 2,4–dinitrophenylhydrazone. b) Liquid film. c) Isolated and characterized as E/Z mixture. d) KBr.

15 selected reflections.

Crystal data of compound (4a): $C_{18}H_{16}O_2$, Mw = 264.324, monoclinic, a = 11.65(1), b = 11.80(1), c = 11.60(2) Å, ß = 114.5(1), U = 1450 Å^3, space group P 2_1/a, Z = 4, Dc = 1.21 g/cm^3, μ(Mo-K$_\alpha$) = 0.8 cm^{-1}, sin θ /λ < 0.63 Å^{-1}, crystal dimensions 0.4x0.5x0.5 mm.

Crystal data of compound (4l): $C_{18}H_{17}NO_2$, Mw = 279.339, monoclinic, a = 8.042(2), b = 9.978(2), c = 19.143(3) Å, ß = 94.61, U = 1531 Å^3, space group P 2_1/a, Z = 4, Dc = 1.21 g/cm^3, μ(Cu-K$_\alpha$) = 6.4 cm^{-1}, sin θ /λ < 0.61 Å^{-1}, crystal dimensions 0.7x0.4x0.07 mm.

The intensity measurements were monitored using three standard reflections, which did not reveal significant variations during the data collections. Of the 2975 unique reflections measured for (4a), and 2543 for (4l), those having I > 2σ (I), 1804 and 2327 respectively, were used for the structure elucidation. The structures were solved by multisolution direct methods with SIR-CAOS[15]. The atomic parameters were refined by block-diagonal (9x9) least-squares calculations; the hydrogen atoms were located on difference Fourier syntheses of electron density, their atomic parameters were kept fixed in the last few cycles of least-squares calculations. The refinements converged to R = 0.047 (Rw = 0.073) and to R = 0.082 (Rw = 0.117) for the crystal structure of (4a) and (4l), respectively.

All the calculations were performed on a Data General MV 8000 II computer, using the crystallographic software SIR-CAOS[15]; atomic scattering factors were taken from literature.[16]

Full lists of atomic coordinates and anisotropic thermal coefficients and tables of bond distances and valence angles, with e.s.d.'s, have been deposited at the Cambridge Crystallographic Data Centre.

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