Palladium-Catalysed Vinylic Substitution of Dimethyl Esters of N-Alkoxycarbonylkainic Acids with Aryl Halides

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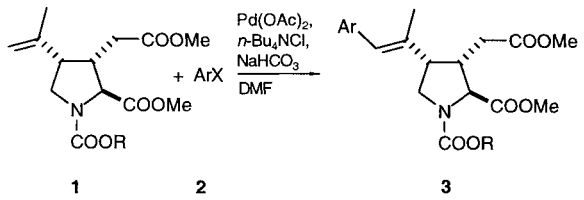
Abstract. The palladium-catalysed reaction of dimethyl esters of N-alkoxycarbonylkainic acids with aryl halides in the presence of catalytic amounts of $Pd(OAc)_2$ and of the *n*-$Bu_4NCl/NaHCO_3$ combination affords stereoselectively the corresponding *E* vinylic substitution products in satisfactory yield.

L-Glutamic acid is the major mediator for neurotransmission of excitatory signals between brain neurones. Hyperactivation of glutamate receptors by excessive extracellular levels of the neurotransmitter is primarily responsible of neuronal damage and death following acute brain demage such as brain ischemia and trauma and may be involved in chronic degenerative diseases as Alzheimer and AIDS dementias. Kainic acid,[1] an exogenous analogue isolated from the seaweed *Digenea simplex* and used because of its insecticidal[2] and anthelmintic[3] properties in Japan, is one of the most potent excitants of mammalian central neurones and can be regarded as a conformationally restricted glutamic acid analogue.

The unsaturated isopropylidene side chain on C-4 is essential for the activity. Kainic acid is an excitatory ligand for glutamate receptors 100-fold more effective than dihydrokainic acid.[4] Extension of the unsaturation through conjugation with a second double bond, as in domoic acid, leads to a further increase of activity.[5] Based on this consideration, Zimmerman *et al.*[6] synthesised a series of kainate antagonists or agonists of presinaptic kainate receptors of potential therapeutic interest through replacement of the isopropylidene methyl by variously substituted phenyl groups. Similarly, Mertes *et al.*[7] had previously modified a protected kainic acid through the palladium-catalysed arylation of the terminal methylene group. Their procedure, however, based on the reaction of the dimethyl ester of N-ethoxycarbonylkainic acid with *m*-nitroaniline and *t*-butyl nitrite in the presence of $Pd(OAc)_2$ (149 mol%), afforded the corresponding aryl derivative as a 2:1 *E/Z* -mixture in only 15% overall yield.

In view of the renewed interest[6] in kainic acids analogues bearing aryl substituents at the isopropylidene chain, we wish to disclose our own results about a more efficient and stereoselective approach to the palladium-catalysed arylation. The aryl derivatives **3**[8] can be obtained through the reaction of dimethyl esters of N-alkoxycarbonylkainic acids **1**[11] with aryl halides in the presence of $Pd(OAc)_2$ (5 mol%) and of the *n*-$Bu_4NCl/NaHCO_3$ combination[12] (Scheme 1). Our results are summarised in the Table.

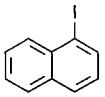


1 2 3

R = Me (**a**), Et (**b**), *t*Bu (**c**)
X = I (60 °C), Br (80 °C)

Scheme 1

Table. Palladium-Catalysed Reaction of Dimethyl Esters of N-Alkoxycarbonylkainic Acids **1** with Aryl Halides.[a,b]

entry	aryl halide **2**	**1** R	reaction time (h)	yield % of **3**[c,d,e]	
1	*p*-MeO-C_6H_4-I	Me	24	68 (26)	**a**
2	"	"	48	28 (52)[f]	"
3	"	Et	"	70 (18)	**b**
4	"	"	"	8 (73)[g]	"
5	"	^{t}Bu	"	27 (56)	**c**
6	*p*-MeCO-C_6H_4-Br	Me	48	47 (37)	**d**
7	*m*-MeCO-C_6H_4-Br	Et	24	47 (29)	**e**
8	*m*-F-C_6H_4-I	Me	46	49 (35)	**f**
9	*m*-O_2N-C_6H_4-I	Et	24	- (90)[h]	**g**
10	"	Me	54	30 (54)	"
11	*p*-Me-C_6H_4-I	"	48	66 (4)	**h**
12	*p*-MeOOC-C_6H_4-I	"	36	36 (33)	**i**
13	*m*-MeOOC-C_6H_4-I	Et	24	42 (24)	**j**
14	*p*-MeCONH-C_6H_4-I	Me	36	41 (37)	**k**
15	*p*-HO-C_6H_4-I	Et	24	31 (57)	**l**
16	*p*-F_3C-C_6H_4-I	Me	46	35 (52)	**m**
17	*p*-OHC-C_6H_4-Br	Et	24	48 (39)	**n**
18	*m*-OHC-C_6H_4-Br	"	"	58 (17)	**o**
19		Me	36	65 (3)	**p**

[a] Unless otherwise stated, reactions were carried out in DMF at 60 °C, by using the following molar ratios: **1**: **2**: $NaHCO_3$: $Pd(PPh_3)_4$ = 1: 1.2: 5: 0.05. [b]Reaction conditions were not optimized. [c]Yields are given for pure isolated products. [d]Figures in parentheses refer to the recovered starting material. [e]All compounds had satisfactory elemental analysis and spectral data were consistent with postulated structures. [f]In the presence of the $KOAc/K_2CO_3$ combination. [g]In the presence of *n*-Bu_3N. [h]In the presence of Et_3N.

Mertes *et al.*[7] proved standard Heck conditions to be unsuccessful. In our hands, the reaction of **1** with *m*-nitrophenyl iodide in the presence of tertiary amines and $Pd(OAc)_2$ led to little conversion (entries 4 and 9), accompanied by substantial recovery of the starting kainic derivative. The $KOAc/K_2CO_3$ combination, reported to give good results in some Heck reactions,[13] gave unsatisfactory results (entry 2). Under Jeffery's conditions[12] dimethyl esters of N-ethoxycarbonyl- and N-methoxycarbonylkainic acids afforded the vinylic substitution products in satisfactory yields. When the more easily removable *t*-butoxycarbonyl- was used as protective group at nitrogen, the yield was strongly decreased (entry 5).

The reaction is seen to be highly stereoselective since the *E* derivatives could be isolated from reaction mixtures containing little if any *Z* isomers. This result was expected on the basis of mechanistic considerations and literature data.[7] The stereochemical outcome of the isolated products, however, was verified by NOE difference studies which showed that vinylic substitution derivatives contained the added aryl unit and the preexisting methyl group on the same side of the carbon-carbon double bond. For example, irradiation of the allylic methyl protons of **3i** produced a 3.45% enhancement of the aromatic H^h protons, but no enhancement of the olefinic H^c proton.

Another point that deserves comment is the integrity of stereogenic centres of **1** under arylation conditions. Indeed, compounds **1** contain one possibly labile stereogenic centre at the position 2 of the pyrrolidine ring and its epimerization could not be *a priori* excluded. Epimerization at the C-2 position under our arylation conditions would require base-catalysed proton abstraction. This process was studied in the allokainic series and it was shown that severe conditions (0.4 N NaOH, 130-140°C, 5 h) were necessary for 50% inversion[14,15] suggesting that epimerization under our conditions is highly unlikely.

In any case, retention of the configuration at C-2 was confirmed by ^{1}H NMR spectra. The pattern of the signals of the pyrrolidine ring protons in N-alkoxycarbonylkainic acid dimethyl esters is substantially retained in the arylation products. Further evidence in favour of the stereochemical stability of the pyrrolidine ring C-H bonds under reaction conditions comes up from the consistency observed in NOE data of **1** and **3**.[16]

In conclusion, we have developed a stereoselective approach to the synthesis of aryl derivatives of kainic acids that affords the desired products in satisfactory yield. It may be an interesting point to make that the conversion of expensive kainic acid derivatives into the desired products is usually high, making it possible to recover and recycle the unreacted material.

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8. Typical palladium-catalysed vinylic substitution of dimethyl esters of N-alkoxycarbonylkainic acids with aryl halides: to a solution of the dimethyl ester of N-methoxycarbonylkainic acid **1a** (0.108 g, 0.35 mmol) and 4-methoxyphenyl iodide (0.122 g, 0.525 mmol) in DMF (1 mL), $NaHCO_3$ (0.116 g, 1.39 mmol), *n*-Bu_4NCl (0.1039 g, 0.35 mmol) and $Pd(OAc)_2$ (0.008 g, 0.035 mmol) were added. The reaction mixture was stirred under argon at 60 °C for 24 h. After cooling, the mixture was diluted with ethyl acetate and washed with water. The organic layer was dried over Na_2SO_4 and evaporated under vacuum. The residue was chromatographed on silica gel, eluting with *n*-hexane/ ethyl acetate (75/25 v/v) to afford 0.142 g (68% yield) of **3a** as a mixture of conformers (NMR analysis; coalescence was reached at 50 °C; DMSO was used as solvent): oil; IR (liquid film) 1745, 1713 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 200 MHz) δ 7.14 (d, J = 8.6 Hz, 2 H), 6.87 (d, J = 8.6 Hz, 2 H), 6.19 (s, 0.5 H, -C-C<u>H</u>=C), 6.17 (s, 0.5 H, -C-C<u>H</u>=C), 4.24 (dd, J = 8.2 Hz, J = 3.2 Hz, 1 H, N-C<u>H</u>), 3.81-3.50 (m, 14 H, C<u>H</u>$_3$O-C(O), C<u>H</u>$_3$O-C(O), C<u>H</u>$_3$O-C(O)-N, C<u>H</u>$_3$O-, N-C<u>H</u>$_2$-), 3.30-3.05 (m, 1 H, =C-C<u>H</u>), 3.05-2.90 (m, 1 H, CH$_3$O-C(O)-C<u>H</u>), 2.55-2.22 (m, 2 H, CH$_3$O-C(O)-C<u>H</u>$_2$), 1.81 (s, 3 H, C<u>H</u>$_3$-C=); ^{13}C-NMR[9] ($CDCl_3$; 50 MHz) δ 172.27 (CH$_3$O-<u>C</u>(O)-CH), 172.16 (CH$_3$O-<u>C</u>(O)-CH$_2$), 158.18 (CH$_3$O-<u>C</u>(O)-N), 155.37 (<u>C</u> aromatic), 154.94 (CH=<u>C</u>-), 132.57 and 132.27 (<u>C</u> aromatic), 130.05 and 129.67 (<u>C</u>H aromatic), 127.14 and 127.05 (<u>C</u>H=C-(CH$_3$)), 113.82 and 113.50 (<u>C</u>H aromatic), 64.01 and 63.76 (<u>C</u>H-N), 55.17 (<u>C</u>H$_3$O-C), 52.73 and 52.49 (<u>C</u>H$_3$O-C(O)-), 51.85 (<u>C</u>H$_3$O-C(O)-N), 47.96 and 47.04 (N-CH$_2$-<u>C</u>H-), 47.67 and 47.43 (<u>C</u>H$_2$-N), 42.44 and 41.41 (CH$_3$O-C(O)-CH$_2$-<u>C</u>H), 33.10 (CH$_3$O-C(O)-<u>C</u>H$_2$), 17.58 (<u>C</u>H$_3$-C=); MS *m/e* (relative intensity) 405 (M$^+$, 7), 284 (55), 258 (22), 198 (32), 173 (100).
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11. Typical preparation of dimethyl esters of N-alkoxycarbonylkainic acids: to a suspension of 0.900 g of kainic acid (4.22 mmol) in 40 mL of *n*-hexane and 40 mL of water, cooled at 0 °C, 1.350 g (16.07 mmol) of $NaHCO_3$ and 0.626 g (6.63 mmol) of MeOCOCl were added. After stirring for 6 h at 0 °C, the reaction mixture was allowed to warm to room temperature, acidified at 0 °C under stirring by dropwise addition of 6N HCl. N-Methoxycarbonylkainic acid was extracted with diethyl ether, washed with water, dried over Na_2SO_4 and methylated by treatment with an excess of freshly distilled ethereal diazomethane at 0 °C for 30 min. After removal of diazomethane excess and evaporation of the solvent under vacuum, the oily residue was chromatographed on silica gel, eluting with *n*-hexane/ethyl acetate (70/30 v/v), to afford 1.13 g of **1** (93 % yield): IR (liquid film) 1737, 1704 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 200 MHz) δ 4.90 (bs, 1 H, <u>H</u>$_2$C=), 4.70 (bs, 1 H, <u>H</u>$_2$C=), 4.15 (dd, J = 6.4 Hz, J = 2.8 Hz, 1 H, C<u>H</u>-N), 3.68 (s, 1.5 H, C<u>H</u>$_3$O-), 3.66 (s, 1.5 H, C<u>H</u>$_3$O-), 3.61 (s, 1.5 H, C<u>H</u>$_3$O-), 3.59-3.42 (bq, J = 6.0 Hz, 2 H, N-C<u>H</u>$_2$), 3.60 (s, 1.5 H, C<u>H</u>$_3$O-), 3.54 (s, 3 H, C<u>H</u>$_3$O-), 2.92 (bq, J = 6.8 Hz, 1 H, =C-C<u>H</u>), 2.80-2.70 (m, 1 H,CH$_3$O-C(O)-CH$_2$-C<u>H</u>), 2.31-2.26 (m, 2 H, CH$_3$O-C(O)-C<u>H</u>$_2$), 1.65 (s, 3 H, C<u>H</u>$_3$-C=); ^{13}C-NMR ($CDCl_3$; 50 MHz) δ 172.24 (CH$_3$O-<u>C</u>(O)-CH), 172.10 (CH$_3$O-<u>C</u>(O)-CH$_2$), 155.36 and 154.93 (CH$_3$O-<u>C</u>(O)-N), 141.03 and 140.77 (<u>C</u>=CH$_2$), 113.35 and 113.19 (C=<u>C</u>H$_2$), 64.01 and 63.70 (<u>C</u>H-N), 52.63 (<u>C</u>H$_3$O-C(O)-CH$_2$), 52.41 (<u>C</u>H$_3$O-C(O)-CH), 51.76 (<u>C</u>H$_3$O-C(O)-N), 47.71 and 47.46 (N-<u>C</u>H$_2$), 45.96 and 45.04 (=C-<u>C</u>H), 41.87 and 40.84 (CH$_3$O-C(O)-CH$_2$-<u>C</u>H), 32.77 (CH$_3$O-C(O)-<u>C</u>H$_2$), 22.32 (<u>C</u>H$_3$-C=); MS *m/e* (relative intensity) 299 (M$^+$, 2), 267 (28), 240 (44), 180 (85), 138 (100).
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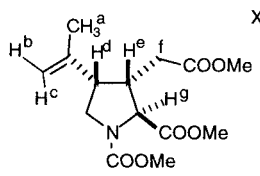
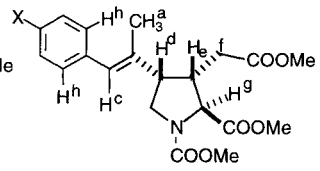


1a



X = *p*-MeO (**3a**), *p*-MeOOC (**3i**)

H_{irr}	**1a** NOE effects (%)						**3a** NOE effects (%)						
	a	c	d	e	f	g	a	c	d	e	f	g	h
a			1.8	1.8		0.9			2.1	2.1		1.3	4.1
d	5.9	2.1		2.9		0.7	10.8	8.4		6.6		2.4	
e			1.3		5.5	7.9			8.6		8.1	11.3	
f			1.4	3.8		7.3			0	5.7		7.8	

17. 10 mg/0.6 mL (**1a:** DMSO-d_6; **3a**: $CDCl_3$); relaxation delay = 10 s; power level = 45 L; irradiation time = 10 sec.