SYNTHESIS OF *N*-ARYLROLIPRAM DERIVATIVES - POTENT AND SELECTIVE PHOSPHODIESTERASE-IV INHIBITORS - BY COPPER CATALYZED LACTAM-ARYL HALIDE COUPLING

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Abstract *– The copper catalysed coupling of rolipram (1) with a wide variety of aryl halides (2) affords N-arylrolipram derivatives (3), potent and selective phosphodiesterase type-IV inhibitors.*

Much attention has been paid to the therapeutic potential of phosphodiesterase (PDE) type-IV inhibitors for the treatment of asthma. This stems primarily from the wide-ranging anti-inflammatory properties exhibited by PDE-IV inhibitors *in vitro* and *in vivo*.[3] The archetypal PDE-IV inhibitor *rolipram* (**1**) suppresses the proinflammatory function of a range of immune cells including mast cells, macrophages, lymphocytes and eosinophils.[4]

Structure-activity studies involving rolipram have implied that its receptor tolerates bulky substituents at the pyrrolidinone nitrogen.[5] In order to exploit this finding we embarked upon the synthesis of a wide range of *N*-arylrolipram derivatives. The requirement of an expedient and general entry into this compound class was apparent. We report herein our results in preparing a large series of mono-, di- and tri-substituted *N*-arylroliprams (**3**). Due to the ready availability of *rolipram* on a large scale,[6] we employed this compound as a starting material and found it an admirably suitable substrate in copper catalysed pyrrolidinone-aryl halide coupling.[7] This proved to be a very versatile procedure for the synthesis of a wide range of *N*-arylrolipram derivatives in moderate to high yields (**Table 1**). *Rolipram* itself was very robust under the reaction conditions, often being partially recovered even after prolonged reaction at high temperature. Furthermore, we were satisfied to observe that subjection of optically pure rolipram enantiomers[8] to the coupling conditions in the presence of 1-iodo-3-(3′-methoxybenzyloxy)benzene (**2i**) provided the corresponding *N*-arylrolipram derivative (**3i**) in good yield with no racemisation at the benzylic carbon (>99% optical purity by chiral HPLC).

Reactions were typically worked up upon completion of *rolipram* consumption, except in cases of prolonged reaction times (>12 h) where unchanged starting material was often recovered. In order to ensure good yields at acceptable reaction rates the appropriate aryl iodides were employed.

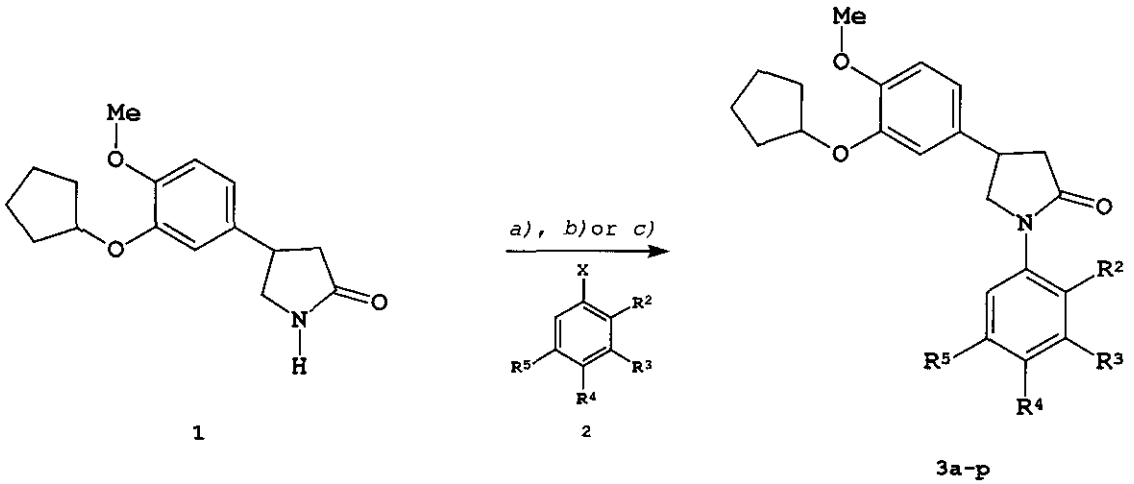
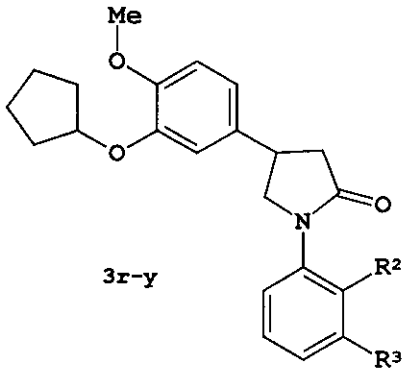


Table 1: Copper catalysed coupling of *rolipram* with aryl halides

Aryl Halide (2)					Conditions	Time (h) / Temp (°C)	Product[9] Yield (%)	MP (°C)
X	R^2	R^3	R^4	R^5				
Br	H	H	H	H	*a)*	3.5 / 150	**3a** (88)	124-126
I	H	OMe	H	OMe[10]	*b)*	4.5 / reflux	**3b** (61)	52-54
I	H	OBn	H	OBn[11]	*b)*	3.5 / 150	**3c** (30)	116-119
Br	NO_2	H	H	H	*a)*	5min / 150	**3d** (90)	117-119
Cl	NO_2	OMe	H	OMe[12]	*a)*	6 / 150	**3e** (32)	Foam
I	H	H	OMe	H	*b)*	6 / reflux	**3f** (16)	75-76
I	H	OBn	OMe	H	*b)*	4 / 150	**3g** (33)	88-89
I	H	OBn	H	H[13]	*b)*	22 / 150	**3h** (50)	103-105
I	H	O(*m*-OMe)Bn	H	H[14]	*c)*	4 / 140	*(+)*-**3i** (81) *(-)*-**3i** (81)	61-62 57-59
I	H	OBn	H	MeO_2C	*a)*	4 / 140	**3j** (59)	Foam
3-Bromo-5-benzyloxypyridine					*a)*	48 / 140	**3k** (74)	117-118
2-Bromo-4-benzyloxypyridine					*a)*	48 / 140	**3l** (54)	101-103
I	H	CO_2Me	H	H	*b)*	16 / reflux	**3m** (70)	129-131
Br	H	NO_2	H	H	*a)*	20 / 150	**3n** (73)	99-101
Br	H	CHO	H	H	*a)*	22 / 135	**3o** (68)	Resin
I	H	O(*m*-OMe)Bn	H	O(*m*-OMe)Bn	*b)*	43 / 140	**3p** (75)	70-75
I	H	Br	H	H	*c)*	18 / 150	**3q** (75)	88-89

Conditions: *a)* Cu(1.85 eq)/K_2CO_3(1.46 eq)/KI(1.56 eq)/aryl halide(2-6 eq)/neat; *b)* Cu(0.16 eq)/K_2CO_3(1.3-1.4 eq)/aryl halide(1.3-1.5 eq)/DMF; *c)* Cu(17-22 eq)/K_2CO_3(1.5 eq)/aryl halide(0.9-1 eq)/DMF

Bromides, and to a lesser extent chlorides (**2e**), were only suitable in the case of bromobenzene (**2a**, no deactivating substituents on the benzene ring) or when electron withdrawing substituents were present in the aromatic ring. Even then coupling was sluggish, albeit in good yield (**3n,o**) unless the activating subs-



3r-y

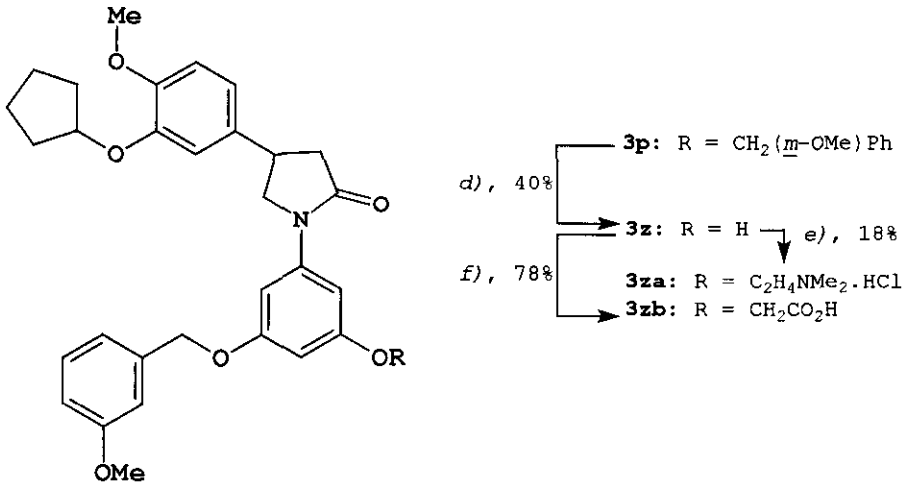
Table 2: Further derivatisation of *N*-arylrolipram derivatives

Arylrolipram			Conditions	Product			Yield (%)	MP (°C)
	R^2	R^3			R^2	R^3		
3d	NO_2	H	H_2/10% Pd-C/MeOH	**3r**	NH_2	H	100	159-161
3h	H	OBn	H_2/10% Pd-C/MeOH	**3s**	H	OH	100	158-160
3n	H	NO_2	1) H_2/10% Pd-C/MeOH 2) ClCO(*p*-OMe)Ph	**3t**	H	NHCO(*p*-OMe)Ph	99	Foam
3o	H	CHO	Ph_3PCH_2(*p*-OMe)Ph/BuLi/THF	**3u**	H	*trans*-CH=CH(*p*-OMe)Ph	33*	163-165
3u			H_2/10% Pd-C/MeOH	**3v**	H	C_2H_4(*p*-OMe)Ph	27 (from **3o**)	91-93
3s	H	OH	NaH/DMF/ClCO(*p*-OMe)Ph	**3w**	H	OCO(*p*-OMe)Ph	73	90-92
3s	H	OH	Cs_2CO_3/IBMK#/80° C/ $ClCH_2$(*p*-OMe)Ph	**3x**	H	OCH_2(*p*-OMe)Ph	57	59-61
3s	H	OH	Cs_2CO_3/IBMK/80° C/ $BrCH_2CO$(*m*, *p*-di-OMe)Ph	**3y**	H	OCH_2CO(*m*, *p*-di-OMe)Ph	80	Resin

* Isolated pure after chromatography. Reaction yield: 83%, 1:1 *cis*:*trans* mixture; # *iso*-butylmethyl ketone

tituent was *ortho* to the bromine. Thus 2-bromonitrobenzene (**2d**) reacted in 90% within 5 min with *rolipram*! Most of the other *rolipram* derivatives prepared had electron rich *N*-aryl substituents. The aryl iodide precursors provided the respective products (**3**) in good yields in these cases except when the deactivating aromatic methoxy group was in the *para* position (**2f,g**). Although not studied in detail, the amount of copper powder used as catalyst had a profound impact on both reaction time and yield, as shown by a comparison of cases **h** and **i**. The dihalide 3-bromoiodobenzene reacted, as expected, preferentially at the iodine-bearing carbon providing *N*-3′-bromophenylrolipram (**3q**) in good yield. Finally, many of the *N*-arylroliprams (**3**) shown in **Table 1** not only proved to be potent and selective PDE-IV inhibitors, but served as starting points for further derivatisation; (**Table 2**). *In vitro* PDE-IV inhibition results indicated, that bulky, lipophilic 3′-mono-, or 3′-,5′- disubstitution at the *rolipram N*-phenyl group significantly improved human neutrophil PDE-IV potency.[15] Such derivatives were either prepared by direct halide coupling; (**Table 1**) or by manipulation of appropriate *N*-arylroliprams; (**Table**

2). However, unsymmetrical *N*-arylroliprams carrying a bulky, lipophilic group in one *meta* position and a polar group to improve aqueous solubility in the other, were particularly interesting from a pharmacological point of view. The synthesis of such derivatives, exemplified by **3za** and **3zb** having unsymmetrical *N*-phenyl 3′,5′-disubstitution posed a selectivity problem. This could be nicely solved by the controlled partial hydrogenolysis of the symmetrical *di*-methoxybenzyl ether (**3p**) in ethyl acetate in acceptable yields,[16] thus obviating the need for more circuitous routes which could not make use of the readily available 3,5-dihdroxyiodobenzene as a precursor.



d): H_2/10% Pd-C/EtOAc *e)*: 1) Cs_2CO_3/IBMK/ClC_2H_4Cl/100°C 2) Me_2NH/EtOH 3) HCl; *f)*: 1) K_2CO_3/$BrCH_2CO_2Me$ 2) NaOH/H_2O/MeOH

Where not commercially available, aryl halide coupling substrates were prepared by standard procedures. 3,5-dimethoxy- (**2b**)[10] and 3,5-dibenzyloxyphenyl iodide (**2c**)[11] are known and the 3,5-di-(3′-methoxybenzyloxy) derivative (**2p**) was prepared in an analogous fashion from 3,5-dihydroyxphenyl iodide by appropriate 3′-methoxybenzylation. The chloro-dimethoxynitrobenzene (**2e**)[12] was prepared by nitration of 3,5-dimethoxychlorobenzene. 3-Benzyloxy-4-methoxyiodobenzene (**2g**) was made from 3-hydroxy-4-methoxyaniline by diazotisation/potassium iodide followed by benzylation, whilst the benzyl ethers (**2h**)[13] and (**2i**)[14] and the methyl ester (**2m**) were prepared from the respective free hydroxy precursor. Finally, the bromopyridines (**2k**) and (**2l**) were synthesised without event using standard methodology from 5-amino-3-bromopyridine[17] and 4-amino-2-bromopyridine respectively.[18]

In summary we have established the copper catalysed pyrrolidinone-aryl halide coupling to be a very useful and general preparation of *N*-aryl substituted derivatives. The reaction works well for phenyl- and pyridyl halide substrates bearing a variety of other aromatic substitution groups and has served as a quick entry by means of which we have been able to synthesise a considerable number of members of this compound class for pharmacological testing.

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