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Carbanion-induced base-catalyzed synthesis of unsymmetrical biaryls from suitably functionalized 2*H*-pyran-2-ones through ring-transformation reactions†

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Abstract—A synthesis of unsymmetrical highly functionalized biaryls with an amino substituent juxtaposed with two nitrile groups in one of the phenyl rings is delineated and illustrated by the carbanion-induced ring-transformation of 6-aryl-4-methylsulfanyl-2*H*-pyran-2-one-3-carbonitrile (**1**) and 4-*sec*-amino-6-aryl-2*H*-pyran-2-one-3-carbonitrile (**2**) to 2-amino-4-aryl-6-methylsulfanyl-1,3-benzodinitrile (**3**) and 2-amino-6-*sec*-amino-4-aryl-1,3-benzodinitrile (**4**) using malononitrile as a source of the carbanion, in moderate yield.

An expedient synthesis of unsymmetrical biaryls, particularly those with hindered rotation, has always been a fascinating and challenging undertaking in natural product chemistry. Arenes with electron donating and accepting substituents are recognized as molecular subunits for displaying non-linear optical properties due to their high polarisability.[1] These molecules not only exhibit optical properties but also display diverse pharmacological activities.[2–6]

Despite numerous approaches to the synthesis of highly functionalized symmetrical and unsymmetrical biaryls, many synthesis have limitations with respect to harshness or functional group intolerance of the conditions required.

Symmetrical biaryls have been prepared by coupling aromatic moieties in the presence of different coupling reagents, for example Ni complexes,[7] arylthallium bis(trifluoroacetate),[8] lithium tetrachloropalladate or ruthenium(IV) tetrakis(trifluoroacetate).[9,10] Recently, palladium-catalyzed cross-coupling between electrophilic compounds Ar–X (X = Br, I, OTf) and organometallic species Ar–M (M being mainly Mg, Zn, Sn and B) has been found to be a versatile route for C–C bond formation.[11,12] Although the synthesis of unsymmetrical biaryls through oxazoline mediated coupling[13] has acquired wide popularity in natural product synthesis, it is limited to certain substituents in the phenyl ring and is restricted by the difficulty in obtaining Grignard reagents. Thus, the need for an improved synthesis of unsymmetrical biaryls was realized with the option of introducing substituents of choice at specific positions either by using the appropriate carbanion reagents or by manoeuvring the substituent in, for example, a 6-aryl-4-methylsulfanyl-2*H*-pyran-2-one-3-carbonitrile (**1**).

Our strategy for the synthesis of unsymmetrical biaryls with electron donating and accepting substituents is based on the base-catalyzed ring-transformation of 4-*sec*-amino-6-aryl-2*H*-pyran-2-one-3-carbonitrile (**2**),[14] obtained from the reaction of 6-aryl-4-methylsulfanyl-2*H*-pyran-2-one-3-carbonitrile (**1**)[15] and a secondary amine. Our initial endeavors with malononitrile failed to affect substitution reactions on **1** and led to a ring transformed compound **3** in lieu of the substituted product. However, the ring-transformation of **2** with malononitrile was very facile and yielded a biaryl with amino substituents juxtaposed with nitrile groups. Compounds with this ring system had been obtained earlier in 10–20% yield[16] as by-product from the reaction of chalcone and malononitrile. Formation of these compounds through ring-transformation may possibly be initiated by nucleophilic attack at C_6, a highly electrophilic center compared to C_4 of the lactone ring due to the extended conjugation and reduction in electrophilicity of C_4 center by the presence of secondary amino group. In this reaction, the initial attack of the

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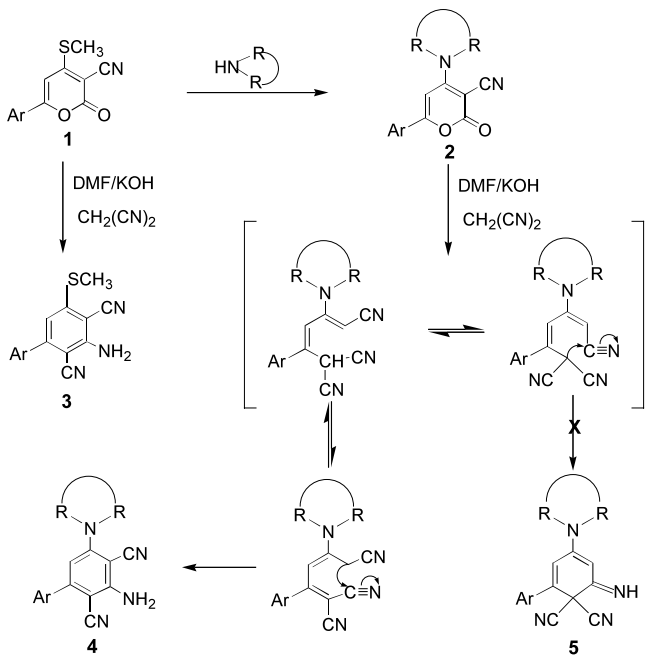
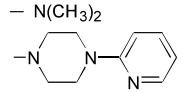
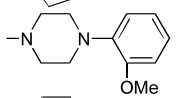
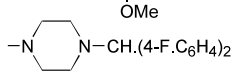
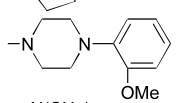
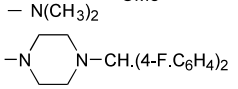
carbanion generated in situ from the malononitrile at C_6 with ring opening is followed by decarboxylation and cyclization to yield the unsymmetrical biaryl which has an amino substituent flanked by two nitrile groups in one of the phenyl rings. There are two possible modes of cyclization after a ring opening and decarboxylation, as depicted in Scheme 1, which would yield either the 2-amino-6-*sec*-amino-4-aryl-1,3-benzodinitrile **4** or the 4-*sec*-amino-2-aryl-6-imino-1,6-dihydro-1,1-dinitrile **5** or a mixture of **4** and **5**. The product isolated from the reaction in moderate yield was characterized by spectroscopic and elemental analyses as the 2-amino-6-*sec*-amino-4-aryl-1,3-benzodinitrile **4**. The structure of one of the compounds, **4a**, was further confirmed by X-ray diffraction. These compounds were prepared by stirring an equimolar mixture of the lactone **2**, malononitrile and powdered KOH in DMF for 20–30 h at room temperature. At the end of the reaction, the reaction mixture was poured into ice water with vigorous stirring and the mixture neutralized with 10% HCl. The crude product was purified by silica gel column chromatography.



4	N(R)(R)	Ar	Yield (%)
a	$-N(CH_3)_2$	4-F.C_6H_4	48
b		4-F.C_6H_4	46
c		4-Cl.C_6H_4	48
d		4-Cl.C_6H_4	44
e		4-Cl.C_6H_4	42
f		4-Br.C_6H_4	50
g		4-Br.C_6H_4	49
h	$-N(CH_3)_2$	4-CH_3.C_6H_4	58
i		4-CH_3O.C_6H_4	42

Scheme 1.

Acknowledgements

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