Iterative Amination Strategy in the Synthesis of Peptidomimetics

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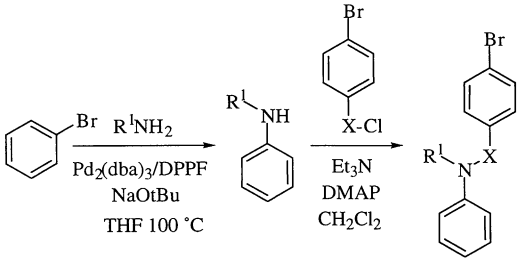
An iterative palladium catalysed cross-coupling reaction of aryl bromides with amines has been employed in the preparation of novel peptidomimetics. This is a versatile strategy with which we can demonstrate the principle of library synthesis by using a diverse range of coupling partners.

The catalytic synthesis of unsymmetrical amine derivatives is of undoubted importance and interest to the chemical community.[1] The independent investigations of Migita,[2] Buchwald[3] and Hartwig[4] developed the palladium catalysed amination of aryl bromides to give aryl amines with aminostannanes. Buchwald and Hartwig[5] have subsequently disclosed new catalytic systems that allow the tin-free, palladium catalysed coupling of aryl bromides with primary amines[6], secondary cyclic amines[7,8] and secondary acyclic amines.[9] The first palladium catalysed amination of aryl chlorides has been noted by Beller.[10]

We wish to report here the successful implementation of an iterative palladium catalysed amination strategy to prepare a small library of peptide analogues by parallel synthesis. For the cross-coupling of primary amines with aryl bromides we employed the combination of $Pd_2(dba)_3$ and dppf (dppf = 1,1'-bis(diphenylphosphino)ferrocene) as catalyst. The $Pd_2(dba)_3$/BINAP catalyst system devised by Buchwald is also effective. In each case good yields of coupled products were obtained (R^1= Ph 95%, $PhCH_2$ 79%), with only trace amounts of products arising from the reduction of the aryl bromide. To enable further amination, we allowed the aniline derivatives to react with *p*–bromobenzoyl chloride or *p*-bromobenzenesulfonyl chloride in the presence of triethylamine to afford linked aryl bromides (up to 99%)(Scheme 1).

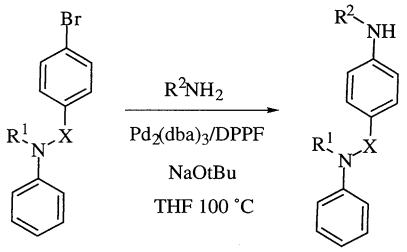


Scheme 1.

The sulfonamide group is a useful replacement for the amide bond in certain peptidomimetics, it is more flexible than an amide and is reported to be more resistant to degradation by proteases.[11]

Extending this strategy further by repeating the amination process enabled us to prepare an array of products with diverse substituents on nitrogen (Scheme 2).

In all cases the amination products were obtained in excellent yield. The effective coupling of *p*-sulfonamide

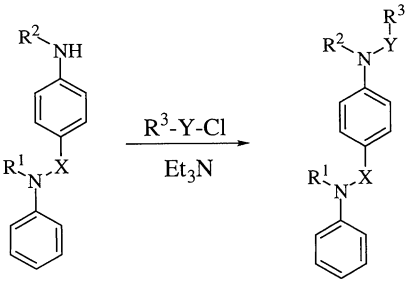


R^1	X	R^2	Yield (%)
Ph	C=O	Ph	95
Ph	C=O	p-$ClC_6H_4CH_2$	81
Ph	C=O	(S)-CH(Me)Ph	80
$PhCH_2$	C=O	$PhCH_2$	91
Ph	SO_2	Ph	77
Ph	SO_2	p-$ClC_6H_4CH_2$	90
Ph	SO_2	(S)-CH(Me)Ph	78
$PhCH_2$	SO_2	$PhCH_2$	95

Scheme 2.

substituted arylbromides with various amines including enantiopure amines extends the scope of the amination process. Given the range of primary amines that are commercially available, this approach offers extensive variability when considering N-aryl coupling.

A further degree of diversification can be achieved by reacting the amine further. In most of the examples shown *p*–bromobenzoyl chloride or *p*-bromobenzenesulfonyl chloride are

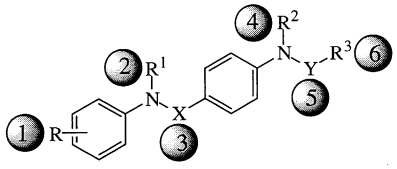


R^1	X	R^2	Y	R^3	Yield (%)
Ph	C=O	Ph	C=O	Ph	80
Ph	C=O	p-$ClC_6H_4CH_2$	SO_2	p-BrC_6H_4	73
Ph	C=O	(S)-CH(Me)Ph	C=O	p-BrC_6H_4	60
$PhCH_2$	C=O	$PhCH_2$	C=O	p-BrC_6H_4	70
$PhCH_2$	SO_2	p-$ClC_6H_4CH_2$	SO_2	p-BrC_6H_4	44
$PhCH_2$	SO_2	$PhCH_2$	SO_2	p-BrC_6H_4	56

Scheme 3.

used, thus providing the potential to further extend the chain (Scheme 3). The products afforded by this sequence resemble the peptoid peptidomimetics. Peptoids are not degraded by important proteolytic enzymes such as papain, chymotrypsin and thermolysin, this has important implications for developing orally active drugs.[12] The synthesis of peptoid libraries, analogous to peptide libraries may facilitate the discovery of new non-peptidic leads.

As illustrated in Scheme 4, the products offer six points of potential diversification including two on nitrogen. We have demonstrated that the palladium catalysed amination protocol is an efficient and effective method for introducing different nitrogen functionality to these positions.



Scheme 4. Sites of potential diversity.

In summary, this simple strategy allows us to rapidly assemble an array of structurally distinct peptidomimetics. It is envisaged that the use of solid-phase synthesis would have a number of advantages over conventional synthesis in solution. [13] Indeed, combinatorial libraries of aniline derivatives on solid support have been assembled employing the palladium catalysed amination reaction.[14] Future work on the construction of larger combinatorial libraries of peptoid derivatives will involve adopting this strategy.

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References and Notes

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