## A Bromoarene Based Approach to Phenylalanine Analogues Hic and Nic

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**Abstract:** A Heck reaction system incorporating  $Ph_4PCl$  and using bromoarenes as substrates has enabled the syntheses of the conformationally constrained phenylalanine analogues Hic and Nic to be dramatically shortened thus facilitating the production of significant quantities of these amino acids.

**Key words:** amino acid synthesis, Heck reaction, phenylalanine analogues, cyclisation, palladium catalysis

Conformationally constrained analogues of amino acids are useful tools in the design of more selective and/or more potent peptides as enzyme inhibitors, and agonists or antagonists at receptors.<sup>2</sup> We recently reported the first syntheses of the conformationally constrained phenylalanine analogues 2,3,4,5-tetrahydro-1*H*-3-benzazepine-2carboxylic acid (Sic), 1,2,3,4,5,6-hexahydro-3-benzazocine 2-carboxylic acid (Hic) and 2,3,4,5,6,7-hexahydro-1*H*-3-benzazonine-2-carboxylic acid (Nic).<sup>3</sup> We have now started to use the amino acids [which form a series of analogues with the well-established phenylalanine substitute 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic)] in biological studies, and have demonstrated that the size of the restricting ring has important consequences for the biological activity of compounds containing the amino acid residues.<sup>4</sup>

In order to fully exploit the potential of Sic, Hic and Nic in a biological context, significant quantities of the amino acids were required. We found that syntheses of multigram quantities of Hic and Nic in particular were hampered, however, by the number of steps in the original approach, (nine and eleven respectively). We wish to report herein that both Hic and Nic may be readily synthesised in multigram quantities using six-step procedures which rely on a versatile intermolecular Heck reaction and a challenging bromoarene-based intramolecular Heck reaction, successfully executed using a recently reported reaction system.

Our original approach to Hic and Nic started with fourand six-step syntheses of iodoaldehydes 1 and 2. Reductive amination of 1 and 2 followed by nitrogen protection and introduction of a carbon-carbon double bond gave iodoarene substrates for Heck cyclisation. After some experimentation, conditions were found which gave good yields of the eight- and nine-membered rings 3 and 4. Finally, hydrogenation and acid hydrolysis of 3 and 4 proceeded in essentially quantitative yield to give Hic.HCl and Nic.HCl.



8 (n = 3)



6 (n = 3)

Table.	Heck reactio	n conditions	applied to	o bromoarene <b>8</b> <i>a</i>
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Entry	Pd(OAc) <sub>2</sub> (mol%)	Solvent (cm <sup>3</sup> )	Temp. (°C)	Time (h)	Base	N <sub>2</sub> /Ar	Other	Yield <b>4</b> (%)	Yield <b>8</b> (%)
1	2.5	DMF (7.2)	110	16	NaHCO <sub>3</sub> (2.5 equiv.)	N <sub>2</sub>	Bu <sub>4</sub> NCl (1 equiv.) 4Å mol sieves	4	77
2	2.5	DMF (7.2)	150	16	NaHCO <sub>3</sub> (2.5 equiv.)	$N_2$	Bu <sub>4</sub> NCl (1 equiv.) 4Å mol sieves	6	27
3	5	DMF (7.2)	120 150	0.5 3.5	NaOAc (2 equiv.)	Ar	Ph <sub>4</sub> PCl (0.3 equiv.)	57	
4	5	DMF (214)	120 150	0.5 4.25	NaOAc (2 equiv.)	Ar	Ph <sub>4</sub> PCl (0.3 equiv.)	69	8
5	5	DMF (7.2)	120 150	0.5 4	NaOAc (2 equiv.)	Ar		<1%	51
6	5	MeOH (1)	130	10	NaOAc (2 equiv.)	Ar	DMG (1 equiv.)	0	88

<sup>a</sup> All reactions were carried out using 0.1 g of 8 except Entry 4 which was performed on a 3 g scale.

In order to shorten the original syntheses, we proposed to replace their early stages with palladium-catalysed couplings between 1-bromo-2-iodobenzene and the three and four carbon units allyl alcohol and 3-buten-1-ol, reactions based on sound literature precedent.<sup>5</sup> Although these reactions, if successful, would give rapid access to bromoaldehydes **5** and **6**, this approach would introduce the non-trivial challenge of using bromoarene based intramolecular Heck reactions to make the medium-sized rings.

In practise, the conversions of 1-bromo-2-iodobenzene to the previously reported bromoaldehyde  $5^6$  and the novel bromoaldehyde **6** proceeded smoothly and were readily performed using 20 g of the arene.<sup>7</sup> (Interestingly, attempts to react 4-penten-1-ol with 1,2-diiodobenzene gave only returned starting material, an observation tentatively attributed to steric resistance to the initial palladium insertion step.) The bromoaldehydes **5** and **6** were then converted into the Heck substrates **7** and **8** using the same methodology as in the original synthesis and in very similar yield.

Heck reactions employing bromoarenes are generally more difficult to effect than those using the corresponding iodides.<sup>8</sup> It was thus not surprising to find that the conditions used for the formation of **4** (in 86% yield) from its iodoarene precursor gave a very low yield (4%) of product when applied to the bromoarene **8** (Table, Entry 1). Raising the reaction temperature from 110 °C to 150 °C, in an attempt to force insertion of palladium into the carbonbromine bond only led to a lower recovery of starting material (Table, Entry 2).

In early 1998, Reetz reported that the use of palladium acetate in the presence of  $Ph_4PCl$  gives high catalytic activity with chloro- and bromoarene substrates.<sup>8</sup> On applying this approach to our substrate, we were delighted to find that bromoarene **8** cyclised to the Nic precursor **4** in 57% yield on a trial scale (Table, Entry 3) and in 69% yield for a typical preparative reaction (Table, Entry 4).<sup>9</sup> As our use of 0.3 equiv. of  $Ph_4PCl$ , the 69% yield of **4**, and our failure to detect phenyl-substituted **8** *i.e.* an aryl scrambling product, were inconsistent with the transfer of aryl groups to the alkene *via*  $Ph_4PCl$  as proposed by Reetz and supported by strong evidence from experiments with chloroarenes,<sup>8</sup> we decided to perform a control experiment without  $Ph_4PCl$  (Table, Entry 5). This gave essentially no cyclisation, indicating that there is a role for  $Ph_4PCl$  in this reaction albeit somewhat different from its role in the catalysis of chloroarene-based Heck reactions.

Later in 1998, Reetz reported that  $Pd(OAc)_2$  in the presence of *N*,*N*-dimethylglycine (DMG) is an effective catalyst of Heck reactions of bromoarenes.<sup>10</sup> Reaction of **8** using a higher loading of  $Pd(OAc)_2$  (5 mol% rather than 1.5 mol%) but with otherwise identical conditions to those reported to give a quantitative conversion of bromobenzene and styrene to Heck products, however, gave only recovered starting material (Table, Entry 6), thus underlining the challenge associated with cyclising bromoarene **8** to the nine-membered ring **4**. Finally, application of the Ph<sub>4</sub>PCl system to bromoarene **7** gave the desired cyclised product **3** in 58% yield, thus facilitating the synthesis of Hic.

In summary, the  $Ph_4PCl$  based Heck system has allowed us to use bromoarenes in the synthesis of Hic and Nic, thus shortening the existing syntheses by three and five steps respectively. The role of  $Ph_4PCl$  in these systems, which appears to be different to its role in chloroarene based reactions, is under investigation.

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- (7) In a typical procedure for the synthesis of 6, a Schlenk tube was charged with 2-bromoiodobenzene (20.000 g, 70.69 mmol), 3-buten-1-ol (7.647 g, 106.04 mmol), sodium hydrogencarbonate (14.855 g, 176.83 mmol), tetra-n-butylammonium chloride (19.696 g, 70.87 mmol) and palladium acetate (0.317 g, 1.41 mmol, 2 mol%). Anhydrous DMF (70 cm<sup>3</sup>) was added and the black reaction mixture saturated with argon. The Schlenk tube was lowered into a preheated oil-bath at 40 °C and heated at this temperature, under an atmosphere of argon, for 20.5 h. After this time, the solution was allowed to cool to room temperature, diluted with diethyl ether (150 cm<sup>3</sup>) and filtered. After evaporation of the solvents under reduced pressure and preabsorption of the red/black oil on SiO2, column chromatography (SiO<sub>2</sub>; hexane-ethyl acetate, 5:1) gave aldehyde 6 as a yellow oil (13.944 g, 61.40 mmol, 87%); (Found: C, 52.8; H, 5.0. C<sub>10</sub>H<sub>11</sub>BrO requires C, 52.88; H, 4.88%);  $v_{max}$ (neat)/cm<sup>-1</sup> 1722vs (C=O);  $\delta_{H}$  (300 MHz) (CDCl<sub>3</sub>) 1.90-2.00 (2 H, m, ArCH<sub>2</sub>CH<sub>2</sub>), 2.44 (2 H, t, J 7, CH2CHO), 2.73 (2 H, t, J 8, ArCH2), 7.00-7.05 (1H, m, H-5), 7.16-7.23 (2 H, m, H-3, H-4), 7.50 (1 H, d, J 8, H-6), 9.72 (1 H, s, CHO);  $\delta_{C}$  {<sup>1</sup>H} (75 MHz) (CDCl<sub>3</sub>) 21.7 (ArCH<sub>2</sub>CH<sub>2</sub>), 34.9 (ArCH<sub>2</sub>), 42.8 (CH<sub>2</sub>CHO), 124.4 (C-1), 127.3, 128.2, 130.2, (C-3, C-4, C-5), 132.6 (C-6) 140.3 (C-2) and 201.9

(CHO); *m*/*z* (CI, NH<sub>3</sub>) 262, 260 (MNH<sub>4</sub><sup>+</sup> + H<sub>2</sub>O - 2H, 100%), 246, 244 (MNH<sub>4</sub>, 40) and 184, 182 (M-CH<sub>2</sub>CHO-H, 41).

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- (9) In a typical reaction, a two-neck r.b. flask fitted with a condenser was charged with thoroughly mixed palladium acetate (0.0871 g, 0.388 mmol, 5 mol%) and tetraphenylphosphonium chloride (0.819 g, 2.18 mmol, 30 mol%) followed by anhydrous sodium acetate (1.197 g, 14.60 mmol). The apparatus was evacuated and purged with argon four times after which a solution of bromoarene 8 (3.002 g, 7.28 mmol) in anhydrous DMF (14 cm<sup>3</sup>) was pipetted into the reaction mixture followed by a further 200 cm<sup>3</sup> of anhydrous DMF. After saturating the solution with argon, the flask was lowered into a silicone oil bath preheated to 120 °C and the reaction mixture heated at this temperature for 30 min under an atmosphere of argon before raising the temperature of the bath to 150 °C and heating for a further 4.25 h when the reaction mixture turned black. The reaction mixture was allowed to cool to room temperature, diluted with diethyl ether (150 cm<sup>3</sup>) and filtered through a short pad of Kieselguhr. After evaporation of the solvents under reduced pressure and preabsorption of the red/brown oil on SiO<sub>2</sub>, column chromatography (SiO<sub>2</sub>; 40-60 petroleum ether - diethyl ether, 2:1) gave the heterocycle 4 as a colourless oil (1.653 g, 4.99 mmol, 69%). The physical data for 4 were identical to previously reported data.2
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