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Radical arylation of tyrosine residues in peptides

Stefanie K. Fehler [a,†], Gerald Pratsch [a,†], Christiane Östreicher [b], Michael C.D. Fürst [a], Monika Pischetsrieder [b], Markus R. Heinrich [a,*]

[a] Department für Chemie und Pharmazie, Pharmazeutische Chemie, Friedrich-Alexander-Universität Erlangen-Nürnberg, Schuhstraße 19, 91052 Erlangen, Germany
[b] Department für Chemie und Pharmazie, Lebensmittelchemie, Friedrich-Alexander-Universität Erlangen-Nürnberg, Schuhstraße 19, 91052 Erlangen, Germany

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ABSTRACT

The radical arylation of the phenolic side chain of tyrosine in peptides was investigated. Aryl radicals were generated from aryldiazonium salts using titanium(III) chloride as stoichiometric reductant. Due to the high selectivity with which 3-aryltyrosine derivatives were formed, this reaction type represents a new strategy for the direct functionalization of peptides.

1. Introduction

Radical arylation reactions have recently become an increasingly popular strategy for the synthesis of biaryl compounds.[1,2] Since such transformations are formally comparable to aromatic C–H activations,[3,4] simple starting materials can be used in comparison with established Suzuki-type cross-coupling reactions.[5] Moreover, good regioselectivities have been obtained in radical arylations of donor-substituted benzenes including phenols[6–8] and anilines.[9] The radical arylation of L-tyrosine,[10] which can essentially be carried out in the complete absence of protecting groups, and which does not lead to partial racemization at the stereocenter of the amino acid thereby represents a particularly valuable alternative to known transition-metal catalyzed protocols.[11] 3-Aryltyrosines prepared through such arylation reactions were recently applied in the synthesis of a highly subtype-selective neurotensin receptor ligand **1** (Fig. 1).[10b,12] The neurotensin receptor subtype 2 (NTS2) appears to be involved in antinociceptive activity and hypothermia, whereas NTS1 is considered to be largely responsible for the control of dopamine-mediated, neuroleptic effects.[13,14] A significant draw-back with regard to a future structural optimization of ligand **1** however is that each hexapeptide has to be prepared separately through multistep solid-phase peptide synthesis (SPPS).[15]

Against this background, it appeared as a challenging task to investigate the direct radical arylation of tyrosine residues in peptides, since this could provide a far easier access to further derivatives of ligand **1** bearing diversely substituted aryl moieties in 3-position of the tyrosine unit. Arylation at the aromatic core of tyrosine incorporated in peptides has so far been achieved through a two-step sequence comprising electrophilic iodination and subsequent Suzuki cross-coupling.[16–18] Since the initial iodination step thereby preferably provides 3,5-diiodinated tyrosines, this strategy is mainly suited for the synthesis of 3,5-diarylated derivatives.

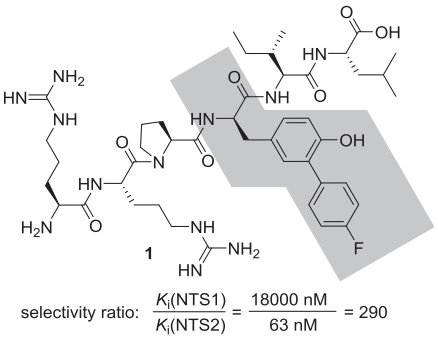

Fig. 1. Neurotensin receptor subtype 2 (NTS2) ligand **1** with high selectivity over NTS1.

* Corresponding author. E-mail address: markus.heinrich@fau.de (M.R. Heinrich).
† These authors contributed equally.

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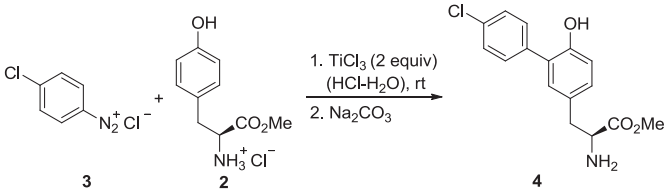
With regard to a selective radical arylation of tyrosine in peptides, which might generally be complicated by the high reactivity of aryl radicals towards many organic functional groups,[19] it was interesting to notice that the backbone of peptides had been found to be largely inert towards the attack of electrophilic hydroxyl radicals.[20] Among all carbon-centered radicals, aryl radicals can also be considered as electrophilic.[21]

In this article, we now report first results on the direct radical arylation of tyrosine residues in peptides and, in particular, on the preparation of further derivatives of NTS2 ligand **1**.

2. Results and discussion

In a first series of experiments, we investigated whether the previously reported titanium(III)-mediated arylation of L-tyrosine methyl ester (**2**) with 4-chlorophenyldiazonium chloride (**3**) (Table 1, entry 1) could also be conducted with substoichiometric amounts of the reductant. Table 1 contains selected results from this series (see Supplementary data for further experiments). Radical arylations of electron-rich benzenes can basically proceed as chain reactions requiring the reductant only as initiator,[7,22] and with regard to an arylation of peptides, lower amounts of titanium(III) would facilitate work-up as well as separation. The yield of 22% from the experiment with 0.1 equiv of titanium(III) chloride demonstrated that a chain transfer does indeed occur (entry 3, 10% theoretical yield for non-chain reaction), but that it is not effective enough to allow for useful conversions of **2**. Addition of zinc to regenerate titanium(III) ions could not improve this result (entry 4). The negative effect of titanium(IV) ions formed in the reaction course became apparent from the reaction reported in entry 5, as the yield was even lower than with 0.5 equiv of titanium(III) chloride (entry 2). Lower amounts of the radical acceptor **2** also decreased the yield to 38% and 31% (entries 6 and 7), which indicated that a good conversion relative to the tyrosine unit will most probably require a significant excess of diazonium ions.

Table 1
Arylation of methyl L-tyrosinate (**2**)

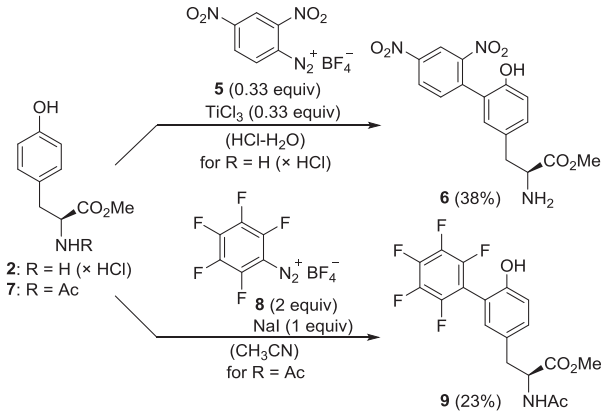


3 (slow addition) **2** (3 equiv) **4**

Entry	Variation of standard conditions[a]	Yield **4** (%)[b]
1	—	56
2	$TiCl_3$ (0.5 equiv)	35
3	$TiCl_3$ (0.1 equiv)	22
4	$TiCl_3$ (0.1 equiv)+Zn (10 equiv)	18
5	$TiCl_3$ (1 equiv)+$TiCl_4$ (1 equiv)	29
6	**2** (1.5 equiv)	38
7	**2** (1 equiv)	31

[a] Standard conditions: Slow addition of **3** (2 mmol) in HCl/H_2O (0.4 M, 5 mL) to a mixture of **2** (6 mmol) and $TiCl_3$ (4 mmol, 4 mL of 1 M soln in 3 M HCl) in H_2O (6 mL) over 10–15 min at rt.
[b] Yield determined by ^1H NMR using dimethyl terephthalate as internal standard.

Radical arylations of arenes are more easy to conduct as chain reactions when electron-deficient diazonium salts are employed.[22] In that case, the diazonium ions are stronger oxidants,[23] and reduction of these can occur along with rearomatization of the cyclohexadienyl adduct arising from the radical addition step.[22] For such reactions, the 2,4-dinitrophenyldiazonium salt **5** and the pentafluoro derivative **8** have been found to be particularly well suited (Scheme 1).[24] Due to good solubility of **5** in water, the

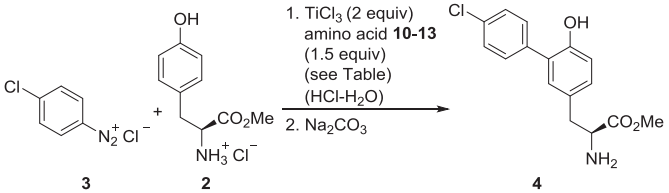


Scheme 1. Arylations with reactive diazonium ions.

arylation of L-tyrosine methyl ester (**2**) could be conducted under conditions comparable to those reported in Table 1. The experiment with the pentafluorophenyldiazonium salt **8**, in contrast, had to be performed in acetonitrile. The use of sodium iodide as initiator had earlier been reported by Kochi.[24] In both reactions, the desired products **6** or **9** were obtained again with high regioselectivity, but not with better yields than those obtained before with the 4-chlorophenyldiazonium salt **3** (Table 1). Interestingly, 3-pentafluorophenyltyrosine derivatives comparable to **9** have not been described in literature so far, although they could be valuable building blocks for investigations by magnetic resonance tomography (MRT).[25]

In further experiments, alternative aryl radical sources, including phenylazocarboxylate salts[26] in the presence of acid and phenylhydrazine in combination with manganese dioxide,[9b] were investigated. Since the comparably low yields of 3-aryltyrosines obtained from these attempts further supported the special aptitude of the reductive conditions based on titanium(III) chloride, we turned to evaluate the effect of other amino acids on the arylation reaction. Based on literature reports and earlier observations, it can be expected that cysteine[27] and methionine[28] have a significant negative impact on radical arylations through either hydrogen atom transfer from the thiol group or homolytic substitution at the sulfur atoms of the thioether. Our study thus focused on phenylalanine **10**, histidine **11**, tryptophan **12** and lysine **13**, which were used as methyl esters in separate competition experiments (Table 2).

Table 2
Competition experiments with amino acid methyl esters



3 (slow addition) **2** (1.5 equiv) **4**

Entry	Competing amino acid[a]	Yield **4** (%)[b]
1	—	38
2	L-phenylalanine methyl ester (×HCl) (**10**)	22
3	L-histidine methyl ester (×HCl) (**11**)	28
4	L-tryptophan methyl ester (×HCl) (**12**)	7
5	L-lysine methyl ester (×HCl) (**13**)	22

[a] Standard conditions: Slow addition of **3** (2 mmol) in HCl/H_2O (0.4 M, 5 mL) to a mixture of **2** (3 mmol), methyl ester-protected amino acid **10**–**13** (3 mmol) and $TiCl_3$ (4 mmol, 4 mL of 1 M soln in 3 M HCl) in H_2O (6 mL) over 10–15 min at rt.
[b] Yield determined by ^1H NMR using dimethyl terephthalate as internal standard.