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Palladium-catalysed allylic amination for the direct synthesis of *epi*-4-alkylamino-*N*-acetylneuraminic acid derivatives

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ABSTRACT

A simple and efficient procedure has been developed for the direct formation of *epi*-4-alkylamino-*N*-acetylneuraminic acid derivatives as potential inhibitors of influenza neuraminidases. The allylic amination of oxazoline **6** has been effected with a series of primary and secondary amines in the presence of catalytic $Pd(\pi\text{-allyl})_2(Et_3P)_2$ to give the corresponding 4-*epi*-alkylamino products in a stereoselective and regiospecific manner.

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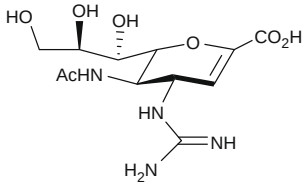
Influenza neuraminidase is an *exo*-glycosidase responsible for the cleavage of terminal *N*-acetylneuraminic acid residues from a host of oligosaccharide substrates which decorate a range of glycoproteins and glycolipids.[1] This enzyme is required by the influenza virus to degrade cell-surface receptor molecules, a process which facilitates the effective release of newly formed viral particles from the surface of infected cells.[2,3] As such, inhibitors of influenza neuraminidases such as Zanamivir **1** and the prodrug Oseltamivir ethyl ester **2**, have proved themselves as effective drugs for the clinical treatment of influenza.[4,5]



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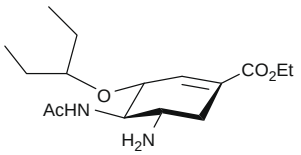

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Compounds **1** and **2** act as competitive inhibitors and were designed to mimic the 'transition-state analogue' 2-deoxy-2,3-didehydro-*N*-acetylneuraminic acid (DANA) **3**, itself a potent inhibitor of influenza neuraminidases (K_m 4 μM).[6] At the heart of the potent inhibitory activity of both **1** and **2** is the introduction of a basic nitrogen at the C-4 position, which is capable of forming an important binding interaction with an anionic aspartate residue in the active site of the enzyme.[7] The importance of this modification was first reported by von Itzstein et al., where 4-amino-2,4-dideoxy-2,3-didehydro-*N*-acetylneuraminic acid **4** (K_m 40 nM) was found to have 100-fold greater inhibitory potency against influenza neuraminidase than DANA **3**.[8] Interestingly, von Itzstein also found that the introduction of an amino group *axial* at C-4 also improved inhibition, with *epi*-4-amino-2,4-dideoxy-2,3-didehydro-*N*-acetylneuraminic acid **5** showing 10-fold greater inhibitory activity (K_m 300 nM) than **3**.[6] This improvement in inhibition was ascribed to potential binding interactions between the axial C-4 amino group and an active-site glutamate residue located above the sugar ring. However, no further studies regarding either the synthesis or biological evaluation of derivatives of **5** have been reported. As part of our interest in the development of novel potent inhibitors of influenza neuraminidases, we have developed a simple and efficient method for the synthesis of *epi*-4-alkylamino derivatives of DANA, to explore further the inhibitory activities of this interesting class of *N*-acetylneuraminic acids.

We have examined the allylic amination of the oxazoline **6** with methylamine using several palladium/phosphine catalysts. Our initial screening revealed that catalysts generated from $Pd_2(dba)_3$ and a variety of phosphine ligands (Et_3P, Me_3P and Ph_3P) did not catalyse the desired amination in reasonable yields. On the other hand, the catalyst generated from $(Pd(\pi\text{-allyl})Cl)_2$ and Et_3P was found to act as a very efficient catalyst with a variety of amine nucleophiles (Table 1). Treatment of **6** with methylamine in the presence of the catalyst (5 mol %) generated from $(Pd(\pi\text{-allyl})Cl)_2$ and Et_3P under standard reaction conditions (dichloromethane, room temperature, 2 h)[9] resulted in stereospecific and regioselective formation of the 4-*epi*-methylamino-*N*-acetylneuraminic acid

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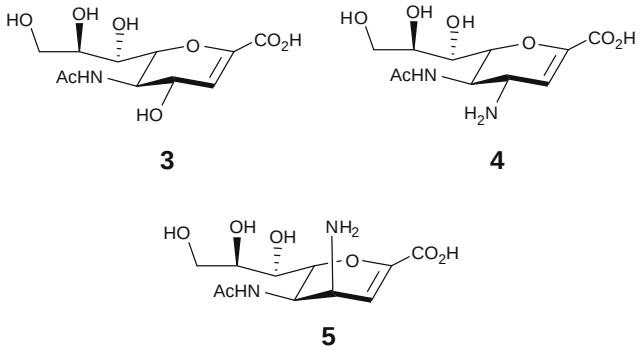


7a in reasonable yield (46%) (entry 1). Compound **7a**[10] was converted to the *N*-sulfonamide **8**[11] for characterisation, with the configuration at C-4 confirmed by ^{1}H NOESY analysis which correlated the C-4 methylamino group and H-6.

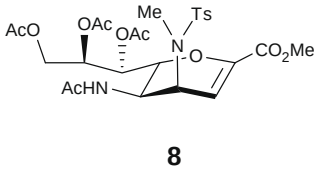


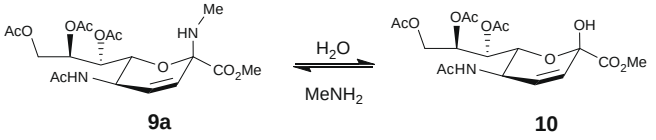
Table 1
Reaction of **6** with various amines and palladium catalysts under standard reaction conditions[9]

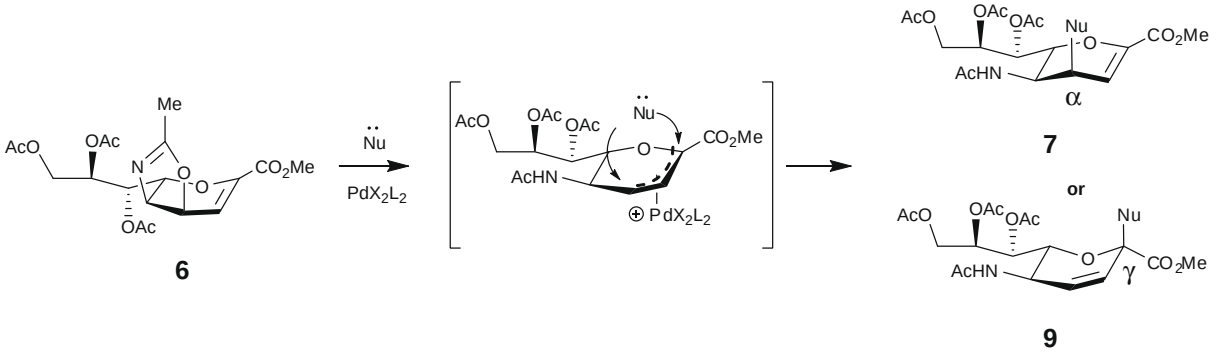
Entry	Amine		Catalyst	Ratio	Yield
	R^1	R^2		7:9	7 + 9 (%)
1	Me	H	$Pd(\pi\text{-allyl})_2(Et_3P)_2$	1:0	46
2	Et	H	$Pd(\pi\text{-allyl})_2(Et_3P)_2$	1:0	75
3	Et	Et	$Pd(\pi\text{-allyl})_2(Et_3P)_2$	1:0	71
4	Me	H	$Pd(\pi\text{-allyl})_2(Ph_3P)_2$	1:10	61
5	Me	H	$(Ph_3P)_4Pd$	1:5	37

This configuration is consistent with the reaction mechanism proposed in Scheme 1, where oxidative addition of the palladium catalyst occurs on the face of the sugar ring opposite to the oxazoline, yielding a (π-allyl)palladium complex with inversion of configuration (Scheme 1). Subsequent nucleophilic attack by the amine also occurs with inversion of configuration to yield products with overall retention of configuration at C-4. When the above-mentioned reaction was repeated for longer periods (overnight), either in the absence of palladium catalyst, or with $(Pd(\pi\text{-allyl})Cl)_2$ present but no phosphine ligand, only starting material was recovered, confirming the requirement for both catalyst and ligand.

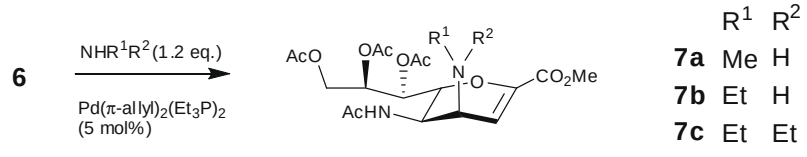
Interestingly, the use of bulkier amines significantly improved the yield of the reactions, whilst retaining the stereospecificity and regioselectivity of amination at the C-4 position. Thus, treatment of **6** with either ethylamine or diethylamine (Scheme 2), in the presence of $[Pd(\pi\text{-allyl})Cl]_2/Et_3P$, yielded the 4-*epi*-ethylamino-**7b**[12] or 4-*epi*-diethylamino- **7c**[13] products in 75% (entry 2) and 71% (entry 3) yields, respectively.

We have also investigated the influence that various phosphine ligands impart on the outcome of the reaction. Increasing the bulk of the phosphine ligand altered the regioselectivity of the reaction, yielding the products of both α- (C-4) and γ- (C-2) amination (Scheme 1). Treatment of **6** with methylamine in the presence of $(Pd(\pi\text{-allyl})Cl)_2/Ph_3P$ gave the products of both α- and γ-amination, **7a** and **9a** in a ratio of 1:10, in reasonable combined yield (61%) (entry 4). On the other hand, treatment of **6** with $(Ph_3P)_4Pd$ gave **7a** and **9a** in a ratio of 1:5 but in significantly lower combined yield (37%) (entry 5). The anomeric configuration of **9a** has not been confirmed but is inferred on the basis of the mechanism described in Scheme 1. Also, the purification of **9a** proved to be difficult and it was considered likely that **9a** was capable of undergoing spontaneous hydrolysis to the hemi-ketal **10**.





Scheme 1. Proposed mechanism for reaction of **6** with amine nucleophiles in the presence of a palladium/phosphine catalyst.



Scheme 2. Reaction of **6** with various amine nucleophiles in the presence of a palladium/phosphine catalyst.

In conclusion, we have developed a simple and effective method to generate novel 4-*epi*-alkylamino-*N*-acetylneuraminic acid derivatives as potential inhibitors of influenza neuraminidases. These derivatives were synthesised directly from the oxazoline **6** through an allylic amination reaction in the presence of $(Pd(\pi\text{-allyl})Cl)_2$/$Et_3P$. Furthermore, this new reaction was shown to be completely stereospecific and regioselective using this catalyst, to give the product of α-amination axial at C-4. However, employing the bulkier catalyst $(Pd(\pi\text{-allyl})Cl)_2$/$Ph_3P$ was found to reverse the regioselectivity of the reaction to yield predominantly the γ-amination (C-2) product.

Acknowledgement

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9. *General reaction procedure*: Phosphine ligand (20 mol %) was added to the palladium catalyst (5 mol %) in deoxygenated CH_2Cl_2 (1.5 mL) and the mixture was stirred at room temperature (30 min). The amine (1.2 equiv) and catalyst solution were then added to **6** in CH_2Cl_2 (1.5 mL) and the mixture was stirred for further 2 h. The mixture was then filtered (Celite®). The Celite® was washed with EtOAc. Chromatography (silica gel, EtOAc→10% MeOH/EtOAc containing 0.5% Et_3N) of the evaporated residue gave the required products.
10. *Compound* **7a**: ^{1}H NMR (400 MHz, CD_3OD): δ 1.94 (s, 3H, NAc); 2.03, 2.04, 2.06 (3s, 9H, OAc); 2.45 (s, 3H, NMe); 3.22 (dd, $J_{3,4}$ = 4.9, $J_{4,5}$ = 9.7 Hz, 1H, H-4); 3.77 (s, 3H, OMe); 4.18 (dd, $J_{8,9}$ = 6.5, $J_{9,9'}$ = 12.6 Hz, 1H, H-9); 4.24 (dd, $J_{4,5}$ = 9.7, $J_{5,6}$ = 9.7 Hz, 1H, H-5); 4.30 (dd, $J_{5,6}$ = 9.7, $J_{6,7}$ = 2.9 Hz, 1H, H-6); 4.57 (dd, $J_{8,9'}$ = 2.9, $J_{9,9'}$ = 12.6 Hz, 1H, H-9′); 5.35 (ddd, $J_{7,8}$ = 6.5, $J_{8,9}$ = 6.5, $J_{8,9'}$ = 2.9 Hz, 1H, H-8); 5.47 (dd, $J_{6,7}$ = 2.9, $J_{7,8}$ = 6.5 Hz, 1H, H-7); 6.17 (d, $J_{3,4}$ = 4.9 Hz, 1H, H-3). ^{13}C NMR (100.59 MHz, CD_3OD): δ 20.65, 20.70, 20.75; 22.71 (C(O)Me); 35.35 (NMe); 47.46 (C-5); 52.75 (OMe); 53.45 (C-4); 63.17 (C-9); 69.49 (C-7); 71.60 (C-8); 74.45 (C-6); 110.77 (C-3); 144.67 (C-2); 163.87 (C-1); 171.58, 172.40, 173.37 (4 C, C(O)Me). HRMS (ESI): calcd for $C_{19}H_{29}N_2O_{10}$ [M+H$^+$]: *m/z* = 445.1817, found: *m/z* = 445.1816; calcd for $C_{19}H_{28}N_2O_{10}Na$ [M+Na$^+$]: *m/z* = 467.1636, found: *m/z* = 467.1631.
11. *Compound* **8**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.01 (s, 3H, NHAc); 2.04, 2.06, 2.10 (3s, 9H, OAc); 2.44 (s, 3H, NArMe); 2.76 (s, 3H, MeN); 3.76 (s, 3H, OMe); 4.12 (dd, $J_{8,9}$ = 7.4, $J_{9,9'}$ = 12.2 Hz, 1H, H-9); 4.17 (br dd, $J_{6,7}$ = 2.2, $J_{5,6}$ = 11.3 Hz, 1H, H-6); 4.47–4.53 (m, 2H, H-4,5); 4.74 (dd, $J_{8,9'}$ = 2.6, $J_{9,9'}$ = 12.2 Hz, 1H, H-9′); 5.28–5.32 (m, 1H, H-8); 5.43 (d, $J_{3,4}$ = 5.2 Hz, 1H, H-3); 5.47 (dd, $J_{6,7}$ = 2.2, $J_{7,8}$ = 4.3 Hz, 1H, H-7); 5.87 (d, $J_{NHAc,5}$ = 9.6 Hz, 1H, NHAc); 7.33 (d, *J* = 8.3 Hz, 2H, Ar); 7.65 (d, *J* = 8.3 Hz, 2H, Ar). ^{13}C NMR (100.59 MHz, $CDCl_3$): δ 20.63, 20.72, 20.85 (C(O)Me); 21.51 (*Me*NArMe); 23.24 (NC(O)Me); 34.67 (MeNTs); 45.39 (C-4); 51.10 (C-5); 52.56 (OMe); 62.18 (C-9); 67.98 (C-7); 71.53 (C-8); 74.06 (C-6); 104.81 (C-3); 127.18, 130.06, 134.80, 144.21 (Ar); 146.49 (C-2); 161.55 (C-1); 169.84, 170.32, 170.54, 170.90 (C(O)Me). HRMS (ESI) calcd for $C_{26}H_{35}N_2O_{12}S$ [M+H$^+$]: *m/z* = 599.1911, found: *m/z* = 599.1904; calcd for $C_{26}H_{34}N_2O_{12}SNa$ [M+Na$^+$]: *m/z* = 621.1730, found: *m/z* = 621.1709.
12. *Compound* **7b**: ^{1}H NMR (400 MHz, CD_3OD): δ 1.12 (t, *J* = 7.3 Hz, 3H, CH_2CH_3); 1.94 (s, 3H, NAc); 2.03, 2.04, 2.06 (3s, 9H, OAc); 2.66–2.82 (m, 2H, CH_2CH_3); 3.30–3.34 (m, 1H, H-4); 3.77 (s, 3H, OMe); 4.18 (br dd, $J_{8,9}$ = 6.6, $J_{9,9'}$ = 12.2 Hz, 1H, H-9); 4.22 (dd, $J_{4,5}$ = 4.8, $J_{5,6}$ = 9.8 Hz, 1H, H-5); 4.29 (dd, $J_{5,6}$ = 9.8, $J_{6,7}$ = 3.1 Hz, 1H, H-6); 4.59 (br dd, $J_{8,9'}$ = 3.1, $J_{9,9'}$ = 12.2 Hz, 1H, H-9′); 5.35 (ddd, $J_{7,8}$ = 6.3, $J_{8,9}$ = 6.6, $J_{8,9'}$ = 3.1 Hz, 1H, H-8); 5.47 (dd, $J_{6,7}$ = 3.1, $J_{7,8}$ = 6.3 Hz, 1H, H-7); 6.16 (d, $J_{3,4}$ = 5.2 Hz, 1H, H-3). ^{13}C NMR (100.59 MHz, CD_3OD): δ 15.33 (CH_2CH_3); 20.65, 20.73, 20.76, 22.73 (C(O)Me); 44.00 (CH_2CH_3); 47.42 (C-5); 51.59 (C-4); 52.76 (OMe); 63.20 (C-9); 69.52 (C-7); 71.70 (C-8); 74.57 (C-6); 111.08 (C-3); 144.64 (C-2); 163.87 (C-1); 171.58, 171.61, 172.39, 173.29 (C(O)Me). HRMS (ESI) calcd for $C_{20}H_{31}N_2O_{10}$ [M+H$^+$]: *m/z* = 459.1979, found: *m/z* = 459.1964; calcd for $C_{20}H_{30}N_2O_{10}Na$ [M+Na$^+$]: *m/z* = 481.1798, found: *m/z* = 481.1785.
13. *Compound* **7c**: ^{1}H NMR (400 MHz, CD_3OD): δ 1.04 (t, *J* = 7.2 Hz, 6H, NCH_2CH_3); 1.94 (s, 3H, NAc); 2.03, 2.03, 2.06 (3s, 9H, OAc); 2.70 (q, *J* = 7.2 Hz, 4H, NCH_2CH_3); 3.51–3.54 (m, 1H, H-4); 3.78 (s, 3H, OMe); 4.16–4.20 (m, 3H, H-5,6,9); 4.60 (br dd, $J_{8,9'}$ = 2.9, $J_{9,9'}$ = 12.4 Hz, 1H, H-9′); 5.34 (ddd, $J_{7,8}$ = 6.5, $J_{8,9}$ = 6.5, $J_{9,9'}$ = 12.4 Hz, 1H, H-8); 5.46 (dd, $J_{6,7}$ = 2.9, $J_{7,8}$ = 6.5 Hz, 1H, H-7); 6.11 (d, $J_{3,4}$ = 5.2 Hz, 1H, H-3). ^{13}C NMR (100.59 MHz, CD_3OD): δ 13.68 ($N(CH_2CH_3)_2$); 20.64, 20.70, 20.73, 22.73 (C(O)Me); 46.96 ($N(CH_2CH_3)_2$); 47.82 (C-5); 52.76 (OMe); 54.65 (C-4); 63.20 (C-9); 69.63 (C-7); 71.79 (C-8); 75.16 (C-6); 110.85 (C-3); 145.14 (C-2); 163.66 (C-1); 171.58, 171.63, 172.42, 173.06 (C(O)Me). HRMS (ESI) calcd for $C_{22}H_{35}N_2O_{10}$ [M+H$^+$]: *m/z* = 487.2286, found: *m/z* = 487.2284; calcd for $C_{22}H_{34}N_2O_{10}Na$ [M+Na$^+$]: *m/z* = 509.2106, found: *m/z* = 509.2106.