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Stille Coupling and One-pot Reduction-Deprotection Sequence in Preparing *Z*-3-(2-Amino-phenyl)-prop-2-en-1-ol, a Precursor in Quinoline Synthesis

Cecilia Devi Wilfred
Chemical Engineering Programme, Universiti Teknologi PETRONAS,
31750 Tronoh, Perak, Malaysia
e-mail:cecili@petronas.com.my

Abstract: Stille coupling on *N*-(2-iodo-phenyl)-acetamide followed by reduction-deprotection sequence has been utilised to prepare *Z*-3-(2-amino-phenyl)-prop-2-en-1-ol (**1**). Consequently, tandem oxidation processes on *Z*-3-(2-amino-phenyl)-prop-2-en-1-ol (**1**) using manganese dioxide was carried out to give quinoline.

Key words: *Z*-3-(2-amino-phenyl)-prop-2-en-1-ol, manganese dioxide, tandem oxidation, quinoline.

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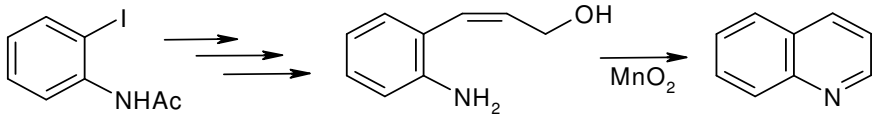
Introduction

Quinolines are known for their anti-malarial properties. Quinine, chloroquinine, amodiaquinine and mefloquinine have been used for malaria chemotheraphy for the past 40 years [1]. The classical methods for quinoline synthesis are (a) condensation of an aniline with a reactant that provides a three carbon unit, traditionally represented by Skraup, Combes and Doebner-Miller syntheses; and (b) condensation of *ortho*-carbon-substituted anilines with a reactant that provides a two-carbon unit to complete the quinoline ring, typically represented by Friedländer, Pfitzinger and Niementowski syntheses [2]. Recently, quinoline was prepared by indium-mediated reductive cyclisation of 2-nitrocinnamaldehyde in aqueous ethanol [3].

In this paper, the synthesis of *Z*-3-(2-amino-phenyl)-prop-2-en-1-ol (**1**) from *N*-(2-Iodo-phenyl)-acetamide by using Stille Coupling and one-pot reduction-deprotection sequence is reported. The compound is then subjected to a tandem oxidation methodology catalyzed by manganese dioxide, where the resulting aldehyde is trapped by the amine present in the molecule with instantaneous cyclisation to form to quinoline. Addition of reagent without isolation of the intermediate **1** makes the sequence more efficient that improve yields. In particular, this applies to aldehydes, which are generally easily hydrated, polymerised, readily decomposed, making their isolation occasionally problematic.



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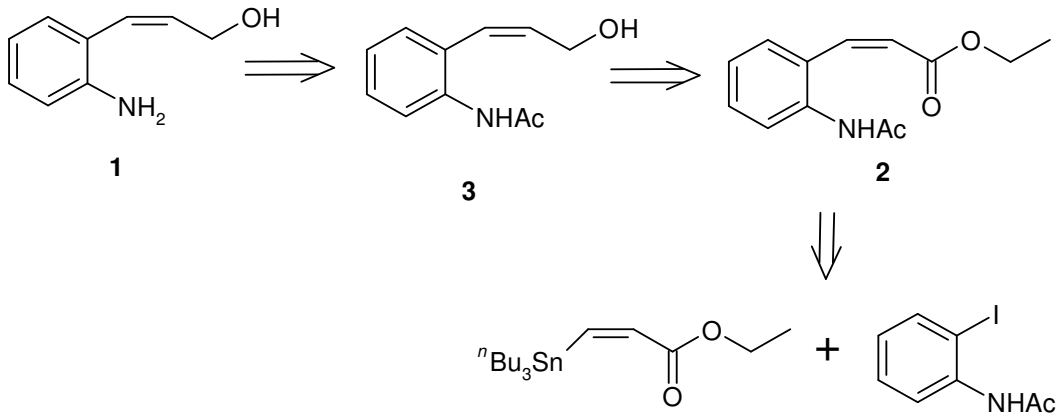
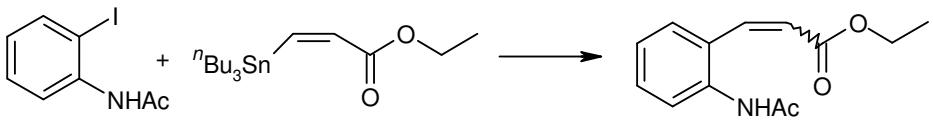
Results and Discussion

The retrosynthetic analysis for *Z*-3-(2-amino-phenyl)-prop-2-en-1-ol (**1**) is as shown in Scheme 1.



Scheme 1 : Retrosynthetic analysis for *Z*-3-(2-amino-phenyl)-prop-2-en-1-ol.



2*Z*, 2*E*
(***Z*** = *Z*-isomer, ***E*** = *E*-isomer)

Table 1: Cross-coupling of *N*-(2-iodo-phenyl)-acetamide with *Z*-vinyl stannane.

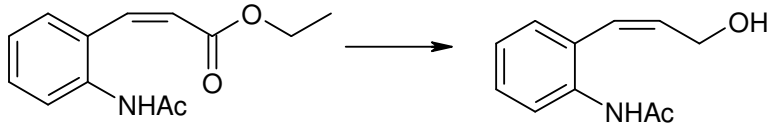
Entry	Catalyst	Conditions*	Yield of compound 2
i.	$Pd(PPh_3)_4$	reflux, 18 h	20 % of *E*-isomer
		rt, 24 h	83 % of *Z*:*E* isomer in a ratio of 1:1
ii.	$PdCl_2(PPh_3)_2$	reflux, 18 h	35 % of *E*-isomer
		rt, 24 h	15 % of of *Z*:*E* isomer in a ratio of 1:1
iii.	$PdBnCl(PPh_3)_2$	reflux, 18 h	18 % of *E*-isomer
		rt, 24 h	23 % of of *Z*:*E* isomer in a ratio of 1:1

* All reactions were carried out using toluene.

Stille cross-coupling of *N*-(2-Iodo-phenyl)-acetamide with *Z*-vinyl stannane was carried out by screening three different catalysts, *i.e* $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$ and $PdBnCl(PPh_3)_2$ in toluene at reflux. The conditions and results of these reactions are shown in Table 1.

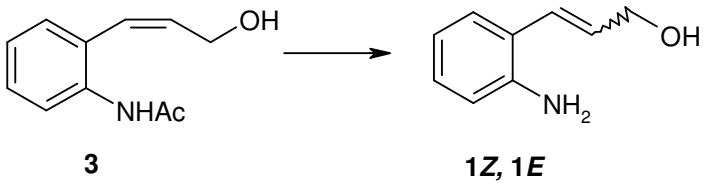
The reactions performed at reflux furnished ethyl (*E*)-3-[2-(acetylamino)phenyl]-2-propenoate (**2*E***) in 20, 35 and 18 % yield, respectively (entry **i, ii** and **iii**). Stille coupling reactions are known to be regio-selective and stereo-selective, preserving the configuration of the coupling partners used to the cross-coupling product [4]. The reaction would have produced the *Z*-isomers of compound **2** as predicted, however high temperature may have isomerised this product to *E*-isomer. We decided to repeat the cross-coupling reactions with each of the catalysts at room temperature. To our delight, stirring the reaction using $Pd(PPh_3)_4$ in toluene at room temperature for 24 hours, gave compound **2** in 83 % yield with a *Z*,*E* ratio of 1:1 (entry **i**). The ^{1}H NMR spectrum showed the *Z*-isomer peaks at δ 7.80 and 6.71 ppm with *J* values of 9.5 Hz, while the *E*-isomer peaks were at δ 8.00 and 6.40 ppm with *J* values of 16.0 Hz. This is the first reported synthesis of two novel compounds. Reactions with $PdCl_2(PPh_3)_2$ and $PdBnCl(PPh_3)_2$ at room temperature, however, gave compound **2** in 15 and 23 % yields, respectively, with *Z*,*E* ratio of 1:1 (entries **ii** and **iii**). The isomers were separated by column chromatography in which *Z*-isomer **2*Z*** eluted first.

Initial attempt to reduce the ester of ethyl (*Z*)-3-[2-(acetylamino)phenyl]-2-propenoate (**2*Z***) with 2.2 equivalents of DIBAL-H or lithium aluminium hydride at 0 ºC, gave 1-*H*-quinolin-2-one. Both reducing reagents deprotected the amide moiety to give amine, which then attacked the ester in a nucleophilic substitution reaction. When the reduction of ethyl (*Z*)-3-[2-(acetylamino)phenyl]-2-propenoate (**2*Z***) was carried out with 2.2 equivalents of DIBAL-H at a lower temperature (-78 ºC) in toluene (Scheme 2), it proceeded to give *Z*-hydroxy-acetamide **3** in 42 % yield after one hour. The ^{1}H NMR spectrum showed the *Z*-isomer peaks at δ 6.80 and 6.52 ppm with *J* values of 11.4 Hz, confirming that the *Z*- geometry has been retained.



2*Z* **3**

Scheme 2 : Reagents and conditions: 2.2 equiv. DIBAL-H, -78 ºC, 1 h, 42 % (*Z*- only).



3 **1*Z*, 1*E***

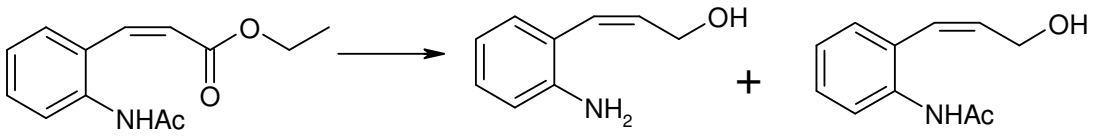
Scheme 3: Reagent and conditions: K_2CO_3 in MeOH, 50 ºC, 48 h, 20 % (*Z*:*E* = 0.6:1).

Ethyl *Z*-*N*-[2-(3-hydroxy-propenyl)-phenyl]-acetamide (**3**) was then deprotected to give *Z*-3-(2-amino-phenyl)-prop-2-en-1-ol (**1**). A methanolic solution of K_2CO_3 was added to compound **3** at room temperature, but after 2 days, only starting material was observed. When we heated the mixture to 50 ºC for 2 days, compound **1** was isolated in 20 % yield (with a *Z*,*E* ratio of 0.6:1) (Scheme 3). The reaction conditions probably favour *E*-isomers formation due to the heating. Separation of the isomeric mixture at this stage was not possible as the two products overlapped on the TLC plate. We also attempted deprotection of the hydroxy-acetamide **3** by adding triethylamine to methanolic solution of K_2CO_3, which gave decomposition products. KOH in methanol and HCl (2 *M* in ether) were also tried in separate reactions, again only decomposition occurred.

An one-pot ester reduction-deprotection was initiated by subjecting ethyl (*Z*)-3-[2-(acetylamino)phenyl]-2-propenoate (**2*Z***) to 2.2 equivalents of DIBAL-H in ether at -78 ºC (Scheme 4). To our delight, this reaction gave amino-alcohol **1** and hydroxy-acetamide **3** in 26 % and 20 % yield respectively, with retention of configuration. We imagine the DIBAL-H had firstly reduced ethyl propenoate **2*Z*** to the hydroxy-acetamide **3** and further deacetylation to amino-alcohol **1**. The ^{1}H NMR spectrum showed the *Z*-isomer peaks of compound **1** at δ 6.48 and 6.00 ppm with *J* values of 11.3 Hz. We had managed to circumvent the deprotection step of hydroxy acetamide **2*Z*** with K_2CO_3, which was problematic. This method proved useful when amide deprotection is difficult (in the presence of ester) and reduction of ester is warranted in the following step, when amine is present.

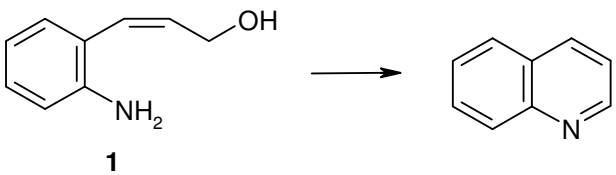
Tandem oxidation-cyclisation quinoline

The synthesis of quinoline with tandem oxidation procedure (Scheme 5) was carried out by treating Z-3-(2-amino-phenyl)-prop-2-en-1-ol (**1**) with 15 equivalents of manganese dioxide in DCM at room temperature. This yielded 38 % quinoline after 1 hour. The quinoline is volatile, therefore some of the compound was probably lost during work up procedures. The ^{1}H NMR spectrum showed aromatic peaks at δ 8.92, 8.21, 8.17, 7.88, 7.75, 7.60 and 7.45 ppm, which are consistent with the published values [5].



2*Z* **1** **3**

Scheme 4: Reagents and conditions: 2.2 equiv. DIBAL-H, Et_2O, -78 ºC, 1 h, **1** = 26 % (*Z*-only), **3**= 20 % (*Z*-only).



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Scheme 5: Reagents and conditions: 15 equiv. MnO_2, DCM, rt, 1 h, 38 % yield.

Experimental

NMR spectra were recorded on a JEOL EX-270 EX-400 instruments using $CDCl_3$ as solvent and tetramethylsilane as an internal standard. Melting points were recorded on a GallenKamp apparatus and the data are uncorrected. IR spectra were recorded on an ATI Mattson Genesis FT-IR or ThermoNicolet IR 100 spectrometer. Low resolution electron impact (EI) spectrum was recorded on a Kratos MS 25 spectrometer. High resolution chemical ionisation (CI) mass spectra were recorded on a Micromass Autospec spectrometer. Flash column chromatography was performed by using silica gel 35-70μ, which was purchased from Fluka. All reagents were purchased from commercial sources and were used without further purification unless stated in the text. Activated manganese dioxide was purchased from Aldrich.

Preparation of Ethyl (*Z*)-3-[2-(acetylamino)phenyl]-2-propenoate (2*Z*) and Ethyl (*E*)-3-[2-(acetylamino)phenyl]-2-propenoate (2*E*). *N*-(2-Iodo-phenyl)-acetamide (0.111 g, 0.42 mmol) and ethyl (*Z*)-3-(tributylstannyl)-2-propenoate (0.198 g, 0.51 mmol) were dissolved in toluene (6 ml) under N_2. $Pd(PPh_3)_4$ (0.010 g, 2 mol %) was added and the mixture was stirred at rt for 24 h. Saturated aqueous KF (2 ml) was added to the reaction and the mixture was stirred vigourously for 1 h. It was then diluted with Et_2O (10 ml), washed with H_2O (2 x 10 ml) and brine (10 ml). The organic extract was dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (PE:EtOAc, 4:1) gave the compound **2*Z*** followed by **2*E***.

Characterisation of Ethyl (*Z*)-3-[2-(acetylamino)phenyl]-2-propenoate (2*Z*) (0.041 g, 42 %) as a colourless oil that solidified at rt, R_f 0.50 (EtOAc:PE, 9:1); ν_{max} (neat)/cm^{-1} 1709 (C=O), 1657 (C=O), 969 (H-C=C); δ_H (400.00 MHz, $CDCl_3$) 11.37 (1H, s, br, NH), 7.80 (1H, d, *J* 9.5 Hz, CH), 7.58 (1H, d, *J* 7.6 Hz, CH), 7.50-7.52 (1H, m, CH), 7.35 (1H, d, *J* 8.1 Hz, CH), 7.23-7.7.25 (1H, m, CH), 6.71 (1H, d, *J* 9.5 Hz, CH), 4.10 (2H, q, *J* 7.1 Hz, CH_2), 2.01 (3H, s, CH_3), 1.26 (3H, t, *J* 7.1 Hz, CH_3); δ_C (100.0 MHz, $CDCl_3$) 169.4 (C), 167.2 (C), 139.7 (CH), 131.2 (C), 129.5 (CH), 128.8 (C), 127.6 (CH), 125.7 (CH), 121.1 (CH), 120.2 (CH), 61.1 (CH_2), 24.6 (CH_3), 14.4 (CH_3); *m/z* (CI) 234 (MH^+ 100%) [HRMS (CI) calcd. for $C_{13}H_{15}NO_3$ (MH^+), 234.1130, found: 234.1129 (0.3 ppm error)].

Characterisation of Ethyl (*E*)-3-[2-(acetylamino)phenyl]-2-propenoate (2*E*) (0.041 g, 42 %) as a colourless oil that solidified at rt, R_f 0.33 (EtOAc:PE, 9:1); ν_{max} (neat)/cm^{-1} 1709 (C=O), 1657 (C=O), 969 (H-C=C); δ_H (400.00 MHz, $CDCl_3$) 11.37 (1H, s, br, NH), 8.00 (1H, d, *J* 16.0 Hz, CH), 7.80 (1H, d, *J* 7.6 Hz, CH), 7.60-7.62 (1H, m, CH), 7.40 (1H, d, *J* 8.1 Hz, CH), 7.08-7.10 (1H, m, CH), 6.40 (1H, d, *J* 16.0 Hz, CH), 4.26 (2H, q, *J* 7.1 Hz, CH_2), 2.35 (3H, s, CH_3), 1.34 (3H, t, *J* 7.1 Hz, CH_3); δ_C (100.0 MHz, $CDCl_3$) 168.8 (C), 166.5 (C), 140.5 (CH), 136.3 (C), 129.6 (CH), 128.4 (C), 128.1 (CH), 126.3 (CH), 124.3 (CH), 123.7 (CH), 61.1 (CH_2), 24.6 (CH_3), 14.4 (CH_3); *m/z* (CI) 234 (MH^+ 100%) [HRMS (CI) calcd. for $C_{13}H_{16}NO_2$ (MH^+), 234.1130, found: 234.1129 (0.3 ppm error)].

Preparation of *Z*-*N*-[2-(3-Hydroxy-propenyl)-phenyl]-acetamide (3). To ethyl (*Z*)-3-[2-(acetylamino)phenyl]-2-propenoate (**2*Z***) (0.0839 g, 0.36 mmol) in toluene (4 ml) under N_2 at -78 ºC, was added DIBAL-H in toluene, *ca.* 1 *M* (0.8 ml, 0.8 mmol) dropwise via syringe for 15 min. After addition was complete, stirring was continued for 1 h. It was then quenched with 20 % w/v Rochelle salt (10 ml). The mixture was left to stir at rt until clear separation of two layers. The organic layer was separated, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (EtOAc:PE, 10:1) gave the compound **3** (0.029 g, 42 %) as a white solid, R_f 0.25 (EtOAc:PE, 9:1); m.p. 101 ºC; ν_{max} (neat)/cm^{-1} 3280 (OH), 1666 (C=O); δ_H (400.00 MHz, $CDCl_3$) 8.02 (1H, d, *J* 8.2 Hz, CH), 7.28-7.31 (2H, m, CH + NH), 7.07-7.13 (2H, m, CH), 6.80 (1H, dt, *J* 11.4, 6.9 Hz, CH), 6.52 (1H, dd, *J* 11.4, 1.5 Hz, CH), 4.19 (2H, dd, *J* 6.9, 1.5 Hz, CH_2), 2.17 (3H, s, CH_3); δ_C (100.0 MHz, $CDCl_3$) 169.0 (C), 135.5 (C), 134.2 (CH), 130.9 (CH), 129.0 (C), 127.9 (CH), 127.8 (CH), 124.8 (CH), 122.8 (CH), 59.9 (CH_2), 25.0 (CH_3); *m/z* (CI) 192 (MH^+ 100%). [HRMS (CI) calcd. for $C_{11}H_{14}NO_2$ (MH^+), 192.1024, found: 192.1026 (1.1 ppm error)].

Preparation of *Z*-3-(2-Amino-phenyl)-prop-2-en-1-ol (1) and *Z*-*N*-[2-(3-Hydroxy-propenyl)-phenyl]-acetamide (3). To ethyl (*Z*)-3-[2-(acetylamino)phenyl]-2-propenoate (**2*Z***) (0.408 g, 1.75 mmol) in Et_2O (12 ml) under N_2 at -78 ºC, was added DIBAL-H in toluene, *ca.* 1 *M* (3.9 ml, 3.9 mmol) dropwise *via* syringe for 30 min. After addition was complete, stirring was continued for 1 h. It was then quenched with 20 % w/v Rochelle salt (10 ml). The mixture was left to stir at rt until clear separation of two layers. The organic layer was separated, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (EtOAc:PE, 10:1) gave compound **1** followed by **3**.

Characterisation of *Z*-3-(2-Amino-phenyl)-prop-2-en-1-ol (1) (0.068 g, 26 %) as a colourless oil that solidified at rt**,** R_f 0.38 (EtOAc:PE, 9:1); ν_{max} (neat)/cm^{-1} 3401 (OH), 1651 (C-NH_2); δ_H (400.00 MHz, $CDCl_3$) 7.10 (1H, dd, *J* 7.6, 1.2 Hz, CH), 6.95 (1H, d, *J* 7.3 Hz, CH), 6.73-6.76 (2H, m, CH), 6.48 (1H, dd, *J* 11.3, 1.5 Hz, CH), 6.00 (1H, dt, *J*

11.3 , 6.7 Hz, CH), 4.23 (2H, dd, *J* 6.7, 1.5 Hz, CH_2), 2.58 (2H, s, br, NH_2); *m/z* (CI) 150 (MH^+ 100%). The spectroscopic data were consistent with those reported [6].

Characterisation of *Z*-*N*-[2-(3-Hydroxy-propenyl)-phenyl]-acetamide (3) (0.066 g, 20 %) as a white solid,**,** R_f 0.25 (EtOAc:PE, 9:1); m.p. 101 °C; ν_{max} (neat)/cm^{-1} 3280 (OH), 1666 (C=O).

Preparation of Quinoline. Manganese dioxide (0.222 g, 2.55 mmol) and 4Å molecular sieves (0.170 g) were added to a solution of *Z*-3-(2-amino-phenyl)-prop-2-en-1-ol (**1**) (0.026 g, 0.17 mmol) in DCM (3 ml). The mixture was stirred at rt under N_2 for 1 h. It was then filtered through a Celite® pad and the cake being washed with excess DCM. The solvent was removed *in vacuo* and the residue was purified by column chromatography (PE:EtOAc: 3:1) to give quinoline (8 mg, 38 %) as a yellow oil, R_f 0.50 (PE:EtOAc:1:1); ν_{max} (neat)/cm^{-1} 1620 (C=N), 1573, 1502, 1432, 1135, 1372, 942 (quinoline ring stretching modes); δ_H (400.00 MHz, $CDCl_3$) 8.92 (1H, dd, *J* 4.0, 1.8 Hz, CH), 8.21 (1H, d, *J* 8.5 Hz, CH), 8.17 (1H, *J* 8.5 Hz, CH), 7.88 (1H, d, *J* 8.2 Hz, CH), 7.77 (1H, dd, *J* 8.5, 7.2 Hz, CH), 7.60 (1H, dd, *J* 8.2, 7.2 Hz, CH_3), 7.45 (1H, dd, *J* 8.5, 4.0 Hz, CH); *m/z* (CI) 130 (MH^+ 100%). The spectroscopic data were consistent with those reported [5].

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