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Synthesis of 2-Oxindole Derivatives *via* the Intramolecular Heck Reaction on Solid Support

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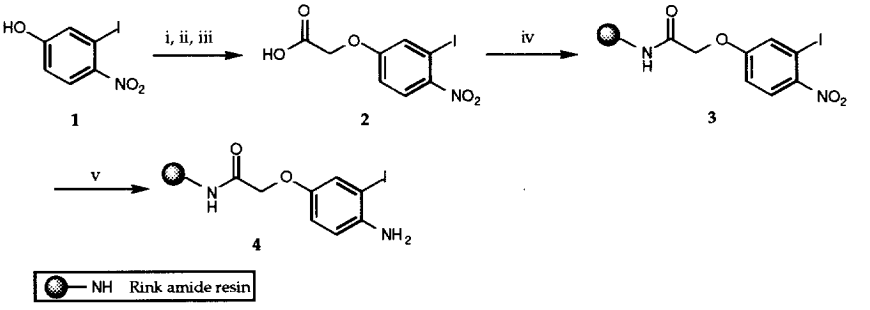
Abstract: Solid phase intramolecular Heck coupling allows the synthesis of 2-oxindoles. Additional diversity is introduced into the molecule by reductive alkylation prior to the Heck cyclisation and also by conjugate addition of a variety of nucleophiles onto the cyclised product prior to cleavage.

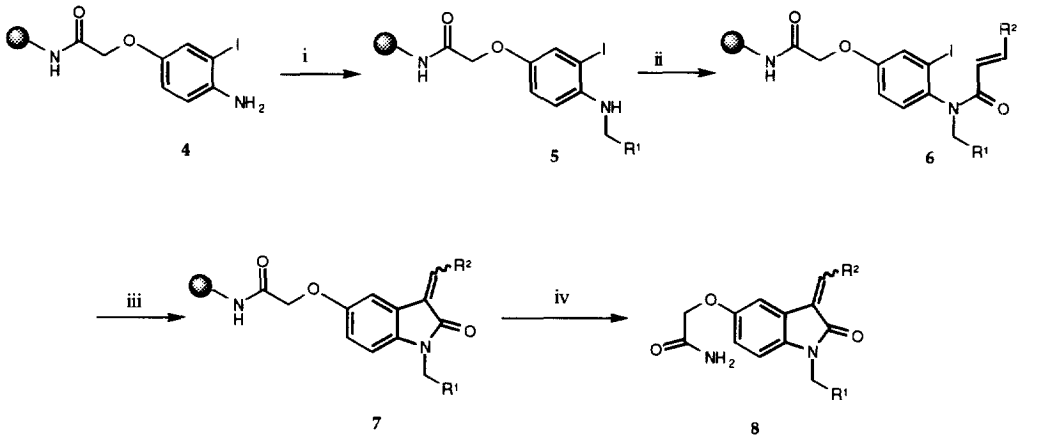
The generation of non-peptide small organic molecules by solid phase methods has been the subject of a great deal of recent attention.[1] There remains a drive to explore new reactions and synthetic routes to molecules of biological interest *via* solid phase approaches. The Heck reaction[2] has proven to be a popular and successful strategy for preparing carbon-carbon bonds on solid phase.[3] The intramolecular Heck reaction[4] is a useful method for forming five, six or seven membered rings fused to aromatic rings. This approach has been applied to the solid phase synthesis of indole[5] and isoquinolinone derivatives.[6] We report the synthesis of 2-oxindole derivatives *via* the intramolecular Heck reaction on solid phase. Oxindoles are known to exhibit anti-rheumatic properties,[7] auxin activity[8] and are inhibitors of mandelonitrile lyase[9] and protein tyrosine kinases (PTK).[10]



1 2 3 4

Scheme 1. i) Ethylbromoacetate (1.1 eq.), K_2CO_3 (1.5 eq.), DMF, 50°C, 3 h, (95%); ii) 1 N NaOH (3.3 eq.), MeOH, reflux, 4 h; iii) Conc. HCl (90%); iv) Deprotected Rink amide resin (0.55 mmol/g), DIC (3 eq.), DMAP (0.1 eq.), NMM (1.1 eq.), DMF, 25 °C, 16 h (quantitative, resin loading = 0.47 mmol/g); v) $SnCl_2.2H_2O$ (8 eq.), DMF, 25 °C, 16 h (70%).

3-Iodo-4-nitrophenoxyacetic acid **2** was prepared by reacting 3-iodo-4-nitrophenol **1** with ethylbromoacetate, followed by hydrolysis of the ester to give the free carboxylic acid. The acid **2** was coupled to deprotected Rink amide resin using diisopropylcarbodiimide (DIC) and 4-N,N-dimethylaminopyridine (DMAP) in DMF at 25 °C. Attempts to reduce the aromatic nitro group of **3** using ferrous sulphate ($FeSO_4.7H_2O$)[11] or sodium dithionate ($Na_2S_2O_4$),[12] proved unsuccessful. Reduction with tin(II) chloride ($SnCl_2.2H_2O$)[13] furnished the resin bound iodoaniline **4** in 70% yield (Scheme 1).[14]



Scheme 2. (yields refer to the case where R^1 = cyclohexyl and R^2 = CH_3). i) R^1CHO (30 eq.), DCM, 25 °C, sonnicate, 15 min; $NaBH(OAc)_3$ (30 eq.), DCM, 25 °C, 16 h, (95%); ii) $R^2CH{=}CHCOCl$ (1.1 eq.), DIPEA (1.1 eq.), DMAP (0.1 eq.), DMF, 60 °C, 16 h, (90%); iii) $Pd(OAc)_2$ (0.3 eq.), Ag_2CO_3 (2 eq.), PPh_3 (0.6 eq.), DMF, 100°C, 16 h, (88%) ; iv) 25% TFA, DCM, 25°C, 16 h, (92%).

Reductive alkylation[15] of aniline **4** with cyclohexanecarboxaldehyde gave the resin-bound secondary amine **5** (R^1 = cyclohexyl) in near quantitative yield (95%) as judged by nitrogen elemental analysis of the dried resin . The secondary amine **5** (R^1 = cyclohexyl) was subsequently acylated with crotonyl chloride to give the tertiary amide **6** (R^2 = CH_3) in 90% yield. Cyclisation of **6** occurred smoothly under Heck conditions[16,17] forming the resin-bound compound 3-ethylidene-2-oxindole **7** (R^1 = cyclohexyl, R^2 = CH_3) in 88% yield. Cleavage from the resin with 25% TFA in dichloromethane afforded 3-ethylidene-2-oxindole **8** (R^1 = cyclohexyl, R^2 = CH_3) in 92% crude yield based on the loading of resin **7** (Scheme 2). The purity of the 2-oxindole **8** (R^1 = cyclohexyl, R^2 = CH_3) was 70 % as judged by HPLC analysis using an evaporative light scattering detector.

The synthesis was expanded using three commercially available aldehydes and three α,β-unsaturated acid chlorides to give six 3-alkylidene-2-oxindoles and three 3-arylidene-2-oxindoles. Excluding the 3-methylene-2-oxindoles, the ^1H NMR spectra of the products showed the presence of two olefinic proton resonances suggesting that both the *(E)*- and *(Z)*-isomers had been formed. The identity and ratios of these isomers were confirmed by ^1H NMR NOSEY and HPLC analysis. Table 1 summarises the yield, purity and *(E) : (Z)* ratios obtained for these compounds. Satisfactory yields were obtained on cyclisation when β−substituted α,β-unsaturated acid chlorides such as crotonyl (R^2 = CH_3) and cinnamoyl (R^2 = Ph) chlorides were used. However, poor results were observed for cyclisation of acryloyl chloride derivatives (**6**, R^2 = H), where the cleaved products showed the presence of high levels of impurities that could not be identified.

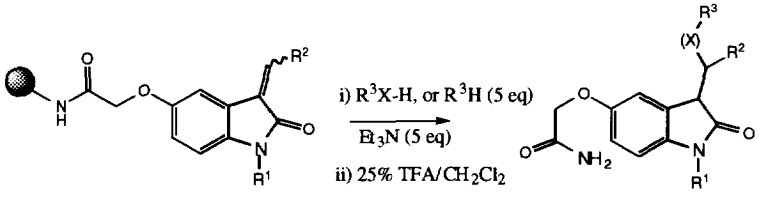
Table 1. Synthesis of oxindole analogues

Entry	R^1	R^2	Yield[a]	Purity[b]	*E:Z*[c]
8a	H	CH_3	91	65	3:1
8b	H	Ph	92	76	5.5:1
8c	H	H	65	10	-
8d	$CH_2C_6H_{11}$	CH_3	92	70	2.7:1
8e	$CH_2C_6H_{11}$	Ph	90	71	5.8:1
8f	$CH_2C_6H_{11}$	H	70	17	-
8g	$CH_2CH(CH_3)_2$	CH_3	90	82	3:1
8h	$CH_2CH(CH_3)_2$	Ph	90	70	5.9:1
8i	$CH_2CH(CH_3)_2$	H	75	16	-

[a] % mass recovered based on initial loading of resin. [b] % Purity refers to the mixture of isomers and was determined by C-18 reverse phase HPLC (20-80% CH_3CN in H_2O containing 0.1% TFA), monitored at 254 nm using a UV detector and by a SEDEX Evaporative Light Scattering Detector. [c] *(E)-:(Z)-* ratio was determined from NOSEY spectra and HPLC chromatograms. All compounds were characterised by ^1H NMR spectroscopy and by mass spectrometry.

1,4 -Conjugate addition of nucleophiles to 7

We have explored the 1,4 addition[18] of soft nucleophiles to the resin-bound oxindole **7** to incorporate an additional component of diversity. Reaction with thiophenol, benzyl mercaptan or diethyl malonate generated the addition product **9** in good yield with moderate to good purity (Table 2).



7 $R^1 = CH_2CH(CH_3)_2$, $R^2 = Ph$ **9**

Table 2

Entry	Nucleophile (R^3XH / R^3H)	Yield[a]	Purity[b]	Diastereoisomeric Ratio[c]
9a	PhSH	90	80	2.5 : 1
9b	$PHCH_2SH$	80	70	2.3 : 1
9c	$(COOEt)_2CH_2$	85	65	1.5 : 1

[a] % mass recovered based on polymer loading. [b] % Purity refers to the mixture of isomers, determined by C-18 reverse phase HPLC (20-80% CH_3CN in H_2O containing 0.1% TFA), monitored at 254 nm using a UV detector and by a SEDEX Evaporative Light Scattering Detector. [c] Determined by HPLC; stereochemical assignments have not been made. All compounds were characterised by ^1H NMR spectroscopy and low resolution mass spectrometry.

To summarise, we have demonstrated that highly functionalised oxindole derivatives of general structure **9** may be synthesised in satisfactory yields and purity on solid phase. Libraries of such compounds may now be generated for biological testing.

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17. **Experimental procedure for the synthesis of oxindole 8d:** Resin bound 3-iodo-4-nitrophenol **3** (0.1 g, 0.0471 mmol, 1 eq.) was reduced with $SnCl_2.2H_2O$ (8 eq.) in DMF (2 ml) at 25 °C for 16 hours to give the 3-iodo-4-aminophenol resin **4**. The resin was filtered and washed (3 x DMF (5 ml), 3 x MeOH (5 ml), 3 x DCM (5 ml)) and dried under high vacuum for 24 hours. Cyclohexanecarboxaldehyde (30 eq.) was added to a suspended solution of **4** (0.1 g, 0.0478 mmol, 1 eq.) in DCM (2 ml) under argon and the reaction was sonnicated for 15 minutes. The resin was washed with anhydrous DCM. A presonnicated solution of $NaBH(OAc)_3$ (30 eq.) was added to the resin and sonnication was resumed for a further 15 minutes. The reaction was allowed to stand at ambient temperature for 16 hours, then washed (3 x DCM (5 ml), 3 x DMF (5 ml), 3 x DMF/H_2O (1:1) (5 ml), 3 x DMF (5 ml), 3 x DCM (5 ml)), and dried under vacuum for 24 hours. Crotonyl chloride (1.1 eq.), DMAP (0.1 eq.), DIPEA (1.1 eq.) were added to the resulting resin bound secondary amine **5** (R^1 = cyclohexyl) (0.1 g, 0.0457 mmol, 1 eq.) suspended in DMF (1 ml) under argon and the reaction mixture was heated at 60 °C for 16 hours. The resin was washed (3 x DMF, 3 x MeOH, 3 x DCM) and dried under vacuum for 24 hours to give the α,β-unsaturated iodoamide **6** (R^1 = cyclohexyl, $R^2 = CH_3$). To effect cyclisation, **6** (0.1 g, 0.0443 mmol, 1 eq.) was treated with $Pd(OAc)_2$ (0.3 eq.), Ag_2CO_3 (2 eq.), PPh_3 (0.6 eq.) in DMF (2 ml) at 100 °C for 16 hours under argon. The resin bound oxindole **7** was washed (3 x DCM (5 ml), 3 x DMF (5 ml), 3 x DMF/H_2O (1:1) (5 ml), 3 x DMF (5 ml), 3 x DCM (5 ml)) and dried under vacuum for 24 hours. The *(E)*- and *(Z)*- 3-ethylidene-2-oxindoles **8** were cleaved by treating with 25% TFA in DCM for 18 hours at ambient temperature.
18. **Experimental procedure for the synthesis of oxindole 9a:** The resin bound oxindole **7** (0.1g, 0.0464 mmol, 1 eq) was suspended in DCM (2 ml). Et_3N (5 eq) was added followed by thiophenol (5 eq) which was added very slowly since the reaction was exothermic. The reaction mixture was shaken at 25° C for 18 hours. The resin was filtered, washed (3xTHF:H_2O (1:1) (5 ml), 3 x H_2O (5 ml), 3 x THF (5 ml), 3 x MeOH (5 ml), 3 x DCM (5 ml)) and dried under vacuum for 24 hours. The oxindole **9a** was cleaved by treating with 25% TFA in DCM for 18 hours at ambient temperature. For the diethyl malonate derivative, conditions were the same except that DMF was used as a solvent and the reaction temperature was 80° C.

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