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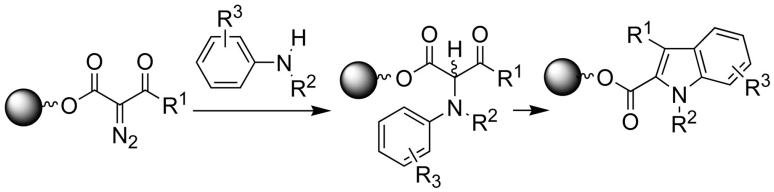

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Solid-Phase Rhodium Carbenoid N−H Insertion Reactions: the Synthesis of a Diverse Array of Indoles

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A solid-phase synthesis of an array of indoles is reported. The key step in our approach involves a N−H insertion reaction of *N*-alkylanilines into a highly reactive polymer-bound rhodium carbenoid intermediate to yield the corresponding α-arylamino-*β*-ketoester. These insertion products were then treated under acid-catalyzed cyclodehydration conditions to yield a series of polymer-bound indole esters, which were subsequently cleaved from the resin under Lewis acid-promoted amidation conditions to yield the desired indoles in good yields and with excellent purities.

Introduction

Combinatorial chemistry is now a widely used technology for the production of libraries of compounds that are subsequently screened for the discovery of biologically active molecules or the further development of biologically active leads.[1] One of the most popular techniques for synthesizing combinatorial libraries uses solid-phase organic synthesis (SPOS).[2] This method is particularly attractive, since isolation of the synthetic intermediates requires only filtration and washing procedures. Because polymer-bound intermediates are easily handled, solid-phase chemistry readily lends itself to automation and has been used to generate very large libraries of compounds using either parallel or split-and-mix synthesis strategies.[1−2] However, solid-phase chemistry does have some drawbacks in that the transfer of standard solution-phase reactions onto the solid phase can be problematic. Despite this, many of the useful reactions from the organic chemists' arsenal have now been optimized for solid-phase conditions.[3] One class of highly useful chemical reactions are those involving diazo-functionalized substrates;[4] however, these compounds have received little attention in the solid-phase arena.[5] This is surprising, considering that diazo-functionalized intermediates are of high synthetic utility, and many of the problems associated with their use in solution (toxicity, light/chemical sensitivity, and dimerization of reactive intermediates) could be potentially suppressed when attached to polymer supports.

In view of this, we recently developed a solid-phase oxazole synthesis[6] using a rhodium carbenoid primary amide N−H insertion strategy.[7] In this approach, a polymer-bound *β*-ketoester was converted into the corresponding α-diazo-*β*-ketoester using standard diazo-transfer conditions. This diazo substrate was treated with a rhodium octanoate catalyst to form a highly reactive rhodium carbenoid intermediate, which subsequently reacts with the primary amide to give the corresponding N−H insertion product. These insertion products are then converted into the desired oxazole heterocycle using a cyclodehydration reaction. One problem encountered during this work was the preparation of diverse polymer-bound *β*-ketoesters; however, we have also developed a general transesterification strategy using *tert*-butyl *β*-ketoesters to prepare these useful polymer-supported intermediates from hydroxyl-functionalized resins.[8] To build on our research in this area, we have investigated the use of these polymer-bound α-diazo-*β*-ketoesters as modular building blocks for the generation of other diverse classes of compounds using a "libraries from libraries"-type format.[9] One particular molecular scaffold of interest are the indoles, since they are known to exhibit a broad range of biological activity. Consequently, there is a large demand for their evaluation as potential drug candidates.[10] Several solid-phase approaches to these molecules have been realized,[10−11] with each method providing synthetic access to indole products bearing different substitution patterns. Still, the preparation of more diversely substituted indoles may lead to the discovery of yet more biologically active compounds, and further research in this area is important. Since there is precedent for the synthesis of these indoles from diazo-functionalized substrates in solution phase,[12] this strategy is an ideal starting point for the elaboration of diverse indole compounds from polymer-bound α-diazo-*β*-ketoester starting materials. Reported herein are our findings for the solid-phase synthesis of indoles using an N−H insertion reaction of a polymer-bound rhodium carbenoid intermediate with an *N*-alkylaniline as the key step. We note that since the completion of this work, an alternative solid-phase indole synthesis using N−H insertion reactions with polymer-bound diazophosphonates has appeared in the literature.[11d]

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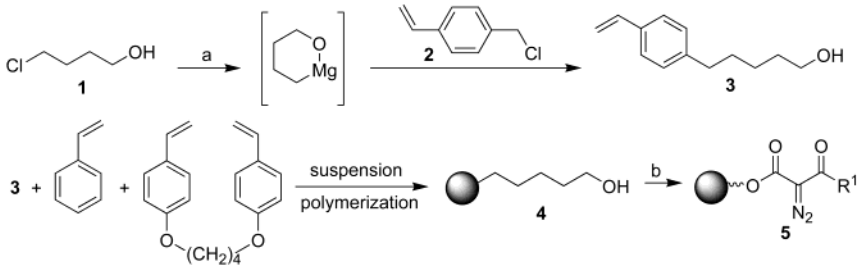
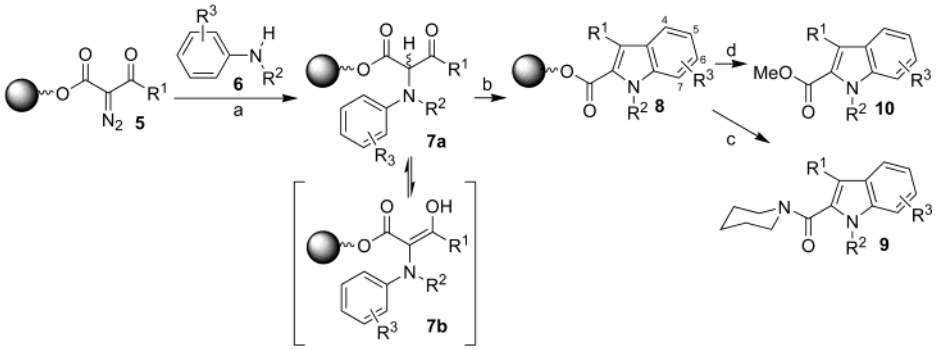
Scheme 1. Preparation of a Hydroxypentyl *J*anda*J*el Resin



(a) i. Isopropylmagnesium chloride (1 equiv), THF. ii. Mg (1.5 equiv), 1,2-dibromoethane (cat.), then add to **2**. (b) i. *tert*-Butyl β-ketoester (3 equiv), toluene, reflux, 6 h. ii. Dodecylbenzenesulfonyl azide (3 equiv), Et_3N (3 equiv), toluene, rt, 16 h.

Scheme 2. Solid-Phase Synthesis of Indoles from Polymer-Bound α-Diazo-β-ketoesters



(a) **6** (10 equiv), Rh_2Oct_4 (2 mol %), toluene, 100 °C, 3 h. (b) *p*-Toluenesulfonic acid (0.1−0.5 M), toluene, reflux, 6 h. (c) Piperidine (10 equiv), $AlMe_3$ (5 equiv), toluene, 110 °C, 16 h. (d) NaOMe (2.5 equiv), MeOH, THF, 50 °C, 1 h.

Results and Discussion

In our original solid-phase oxazole synthesis,[6] a hydroxybutyl-functionalized *J*anda*J*el resin that was synthesized from the corresponding chloromethyl resin according to literature precedent[13] was utilized as the solid support. Although this resin was of acceptable quality, much of the work from our laboratory has centered on the preparation of polymer supports that require little or no chemical modification before the planned synthesis.[14] This is important, since the potential for unwanted impurities within the resin from either unreacted functional groups or from the reagents used to convert the various functional groups is eliminated. It also follows that the more manipulations performed on a resin before a planned synthesis, the higher the likelihood of fragmentation and damage to the resin bead structures. The presence of such chemical impurities was a particular issue with the hydroxybutyl resins prepared using an allylation/hydroboration series of reactions on chloromethyl resins, since the boron impurities from the last step were particularly difficult to remove. Because of these potential problems, an alternative strategy for the preparation of hydroxyalkyl resins was devised. In this approach, a 4-(5-hydroxypentyl)styrene **3** was prepared in one step by the reaction of the Normant−Grignard reagent[15] with 4-vinylbenzyl chloride **2** (Scheme 1). The corresponding hydroxypentyl-functionalized *J*anda*J*el resin **4** was then prepared from monomer **3**, styrene, and cross-linker using standard suspension polymerization procedures.[16] The α-diazo-β-ketoester starting materials **5** were prepared from this resin according to our recently published protocols.[8]

The preliminary N−H insertion and indole formation reactions were investigated using the methyl-substituted α-diazo-β-ketoester (**5**, R^1 = Me) and *N*-methylaniline (**6**, R^2 = Me, R^3 = H) (Scheme 2). In the case of the N−H insertion reaction, many different conditions were investigated before an acceptable method was found. For example, when conditions similar to those developed by Moody[12] were applied (∼1 equiv aniline, 2 mol % rhodium catalyst, chloroform or toluene, reflux), the yield of insertion product **7** was poor (as estimated by mass balance), and IR analysis of these products revealed a broad, strong absorption at 1720 cm^{-1}. Additional experiments showed that as the yields of insertion product improved, the intensity of this absorption diminished, and we postulated that this IR signal was from an unwanted side product rather from than the desired insertion product **7**. These findings were corroborated by performing the insertion reaction in the absence of *N*-methylaniline, and a product was indeed produced that exhibited the intense IR absorption at 1720 cm^{-1}. With this in mind, the success of each subsequent insertion reaction was assessed by the absence of this unwanted absorption in IR spectra of the product **7**. Additionally, further analysis of the IR spectra of the insertion products **7** and also IR and NMR spectra of solution-phase analogues (lack of ketone carbonyl, the presence of a weak OH stretch in the IR, and the presence of an enol proton in the ^1H NMR) lead to the conclusion that the insertion product exists as its tautomer **7b**, rather than the α-arylamino-β-ketoester **7a**. To optimize the insertion reaction, several variables, including the amount of aniline **6**, the type of solvent, and the reaction temperature, were investigated. The first experiments using larger quantities of *N*-methylaniline **6** showed that the unwanted side reaction could be somewhat suppressed. However, the use of a large excess of the aniline **6** in the reaction slowed the

reaction of the diazo substrate **5** considerably, as estimated by IR (disappearance of C═N═N absorption at ∼2140 cm^{-1}). The best conditions found were 10 equiv of *N*-methylaniline; when quantities up to 40 equiv were used, no further improvement of product quality was observed. Of the solvents examined, polar solvents, such as dimethylformamide (DMF) and dimethylacetamide (DMA), gave poor yields of product, whereas 1,1,2,2-tetrachloroethane gave similar results when compared with toluene.

The next variable investigated was reaction temperature. Since a large excess of the aniline component in the reaction retarded the rate of the reaction, the effect of higher reaction temperatures was investigated. When the reaction was performed at 80 °C, IR analysis showed complete consumption of starting materials after 3 h. Increasing the temperature to 110 °C reduced the reaction time considerably (0.5 h), but both of these conditions furnished products **7** with similar quality, as estimated by IR. During these experiments, an interesting effect of the temperature at which the catalyst was added to the reaction was observed. Typically, the resin-bound substrate **5**, the aniline **6**, and the catalyst were first combined in toluene and then heated to the desired temperature. However, improved results (i.e., a reduced quantity of unwanted side products observed by IR) were obtained when a mixture of the resin-bound substrate **5** and 5 equiv of the aniline **6** in toluene were first combined and then heated to 100 °C before addition of a second solution containing the catalyst (2 mol %) and 5 equiv of the aniline **6** in a small volume of toluene. This phenomenon was less significant in cases of R^1 = aryl, but this optimal procedure was critical for success when R^1 = alkyl, and especially when R^3 was an ortho substituent.

With an optimized set of conditions for the solid-phase rhodium-catalyzed aniline N−H insertion reaction established, the conversion of the insertion products **7** into the desired indole heterocycle **8** and the cleavage of the products from the resin was examined (Scheme 2, Table 1). Inspired by Moody's findings[12] that strong acid ion-exchange resin gave superior results for the conversion of α-arylamino-*β*-ketoesters into the desired indoles over other methods (such as Lewis acid-mediated cyclodehydration), the conversion of **7** to **8** was investigated using *p*-toluenesulfonic acid (TsOH). In this approach, anhydrous solutions of TsOH in toluene were prepared from the corresponding hydrate by azeotropic removal of water using a Dean−Stark apparatus. The polymer-bound insertion products **7** were then treated with these solutions (0.1, 0.25, and 0.5 M) at reflux for several hours, and the rate of conversion to the polymer-bound indole **8** was estimated by IR spectroscopy (disappearance of α,*β*-unsaturated ester **7** at ∼1640 cm^{-1} and appearance of the indole ester **8** at ∼1700 cm^{-1}). Of the 13 polymer-bound α-diazo-*β*-ketoesters examined (entries 1−13), 10 were successfully converted into the final indole products. The R^1 substituents that did not work were 3,4-methylenedioxyphenyl, *N*-methylindol-2-yl, and trifloromethyl (Table 1, entries 7, 11, and 13). When R^1 was an alkyl group, the cyclization using 0.10 M TsOH was complete within 6 h. However, when R^1 was an aryl group, the cyclization reaction was slower, and higher concentrations of TsOH (0.25 M) were required to ensure complete conversion of **7** to **8** within 6 h. No discernible difference in the rate of the cyclization reaction between either electron-rich or electron-deficient aryl R^1 groups was observed.

The effect of *N*-(R^2) and aryl-(R^3) substituents in both the insertion and the cyclization reactions was also examined. When the N-substituent R^2 was an alkyl group (eg., Me, Et, Bu), both the insertion reaction and cyclization proceeded smoothly. Although N-unsubstituted aniline (R^2 = H) and *N*-allylaniline (R^2 = allyl) were good substrates in the insertion reaction, attempts to convert these intermediates **7** into the desired indoles **8** failed (entries 18 and 19). It is noted that tetrahydroquinoline was used successfully in the insertion reaction, and this product was smoothly cyclized and cleaved from the resin to give the corresponding tricyclic indoles **9** in good yield and purity (entries 14 and 35). Although indoline was a successful partner in the insertion reaction, its insertion product **7** could not be converted into the corresponding indole (entry 15). Benzyl N substituents (R^2) were also tolerated in the insertion reaction, and after cyclization under the mild conditions (0.10 M TsOH, R^1 = Me), the corresponding *N*-benzyl indole **9** was isolated from the resin in modest yield (entry 21). However, when R^1 = 4-CF_3−Ph and R^2 = Bn, the harsher cyclization conditions (0.25 M TsOH) required for cyclization resulted in partial debenzylation of indole product **8**, and lower yields of the cleaved material **9** were obtained (entry 42). The bulky anilines, such as *N*,*N*-diphenylamine, *N*-ethyl-1-naphthylamine and also *N*-hydroxyethyl aniline, were poor substrates for the insertion reaction (entries 20, 34, and 22).

The aryl substituents (R^3) of the aniline building blocks had the most dramatic effect on the outcome of indole formation. Although most R^3 groups were tolerated in the insertion reaction, the electronic properties imposed by R^3 on the aryl group and also the substitution pattern of R^3 had a significant affect upon the rate of conversion of the insertion products **7** into the indoles **8**. In general, when R^3 was an electron-donating group, the cyclization proceeded smoothly. However, when R^3 was ortho to the nitrogen or an electron-withdrawing group, harsher conditions were required to achieve complete conversion to indole **8**. For example, when R^1 = Me, most of the insertion products **7** were converted into the desired indoles **8** within 6 h using only 0.10 M TsOH. However, when R^1 = Me and R^3 was a nitro group (entry 27) or an ortho substituent (entries 28−32), these substrates required higher concentrations of TsOH (0.25 M) for complete conversion to the indole **8** within 6 h. This trend became even more apparent when R^1 = aryl, the preparation 5-nitroindole (R^1 = 4-CF_3−Ph, entry 43) required the concentration of TsOH to be increased to 0.5 M, and the reaction time was extended to 48 h to achieve complete conversion of **7** to **8**.

The effect of trifluoromethanesulfonic acid (triflic acid) in place of TsOH was investigated in model solution-phase cyclization experiments, and it enhanced the rate of conversion of **7** to **8** in these stubborn cases. Unfortunately, these conditions were incompatible with the solid-phase reaction, because the *J*anda*J*el resin was not stable to this reagent.[17] Finally, the effect of microwave heating[18] in the cyclization

Table 1. Examples of Indoles Prepared by Rhodium Catalyzed Solid-Phase N−H Insertion Strategy

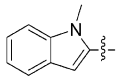
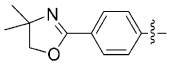
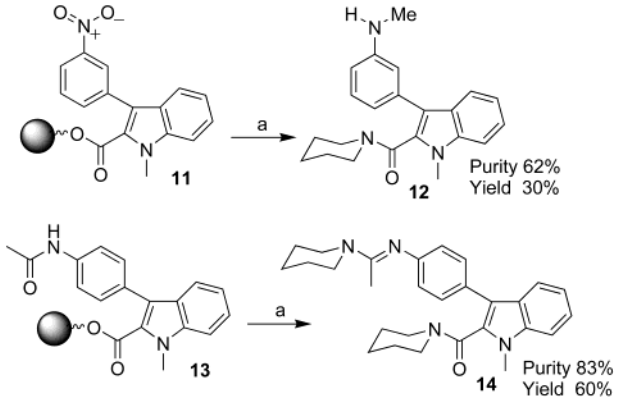
Entry	Product	R^1	R^2	R^3	[TsOH]/M	Purity[a] (%)	Yield[b] (%)
1	**9**	Me	Me	H	0.10	72	35
2	**9**	*n*-Pr	Me	H	0.25	82	29
3	**9**	4-MeO-Ph	Me	H	0.25	97	60
4	**9**	4-F-Ph	Me	H	0.25	98	65
5	**10**	3-NO_2-Ph	Me	H	0.25	94	51
6	**9**	4-CF_3-Ph	Me	H	0.25	96	72
7	**9**	3,4-methylene-dioxy-Ph	Me	H	0.25	-	0
8	**9**	4-(dimethyl-amino)-Ph	Me	H	0.25	85	18
9	**10**	4-acetamido-Ph	Me	H	0.25	76	63
10	**10**	5-acetamido-*n*-pentyl	Me	H	0.25	83	44
11	**9**		Me	H	0.25	-	0
12	**10**		Me	H	0.25	83	67
13	**9**	CF_3	Me	H	0.25	-	0
14	**9**	Me	1,7-$(CH_2)_3$-		0.10	79	31
15	-	Me	1,7-$(CH_2)_2$-		0.25	-	0
16	**9**	Me	Et	H	0.10	76	34
17	**9**	Me	*n*-Bu	H	0.10	89	33
18	-	Me	allyl	H	0.25	-	0
19	-	Me	H	H	0.25	-	0
20	-	Me	Ph	H	0.25	-	0
21	**9**	Me	Bn	H	0.10	88	40
22	-	Me	$HO(CH_2)_2$-	H	0.25	-	0
23	**9**	Me	Me	5-MeO	0.10	85	27
24	**9**	Me	Me	5-Et	0.10	93	48
25	**9**	Me	Me	5-Cl	0.10	91	60
26	**9**	Me	Me	5-Br	0.10	85	51
27	**10**	Me	Me	5-NO_2	0.25	93	55
28	**9**	Me	Me	7-Me	0.25	85	20
29	**9**	Me	Me	7-MeO	0.25	89	25
30	**9**	Me	Me	7-Cl	0.25	95	40
31	**9**	Me	Me	6,7-di-Me	0.25	87	38
32	**9**	Me	Me	5,7-di-Cl	0.25	89	25
33	-	Me	Me	7-NO_2	0.25	-	0

Table 1 (Continued)

34	-	Me	Et	6,7-(C_4H_4)-	0.25	-	0
35	**9**	4-CF_3-Ph	1,7-(CH_2)$_3$-		0.25	96	65
36	**9**	4-CF_3-Ph	Et	H	0.25	96	71
37	**9**	4-CF_3-Ph	Bu	H	0.25	95	58
38	**9**	4-CF_3-Ph	Me	5-MeO	0.25	94	67
39	**9**	4-CF_3-Ph	Me	5-Et	0.25	97	80
40	**9**	4-CF_3-Ph	Me	5-Cl	0.25	88	82
41	**9**	4-CF_3-Ph	Me	5-Br	0.25	92	81
42	**9**	4-CF_3-Ph	Bn	H	0.25	55	31
43	**10**	4-CF_3-Ph	Me	5-NO_2	0.50[c]	64	36

[a] Purity of crude compound assessed by HPLC at 254 nm. [b] Yield of purified material based upon loading of resin **5**. [c] Reaction time, 48 h.

Scheme 3. Unexpected Side Reactions During the Amidation Cleavage Reaction.



(a) Piperidine (10 equiv), $AlMe_3$ (5 equiv), toluene, 110 °C, 16 h.

reaction was examined (toluene−dichloroethane solvent mixtures were used). Although the reaction times were reduced, the purity of the products obtained after cleavage was inferior to those prepared using conventional heating.

The polymer-bound indoles were cleaved from the resin using either a diversity-building amidation reaction[19] to give the indole-2-carboxamide **9** or a transesterification reaction to give the methyl indole-2-carboxylate **10 (**Scheme 2). For the amidation reaction, our standard conditions (6 equiv of amine, 2 equiv of $AlCl_3$, CH_2Cl_2, rt)[6,8] failed to give any cleavage products. However, the use of $AlMe_3$ (10 equiv of amine, 5 equiv of $AlMe_3$) at 110 °C in toluene gave the desired cleavage products within a few hours. After cleavage, each of the crude amide products **9** was passed through a short pad of strong acid/strong base mixed-bed ion-exchange resin (∼2 cm^3) and Florisil (∼1 cm^3), and their purity was estimated by analytical HPLC. The crude products were then further purified by preparative TLC to give final isolated yields of products **9** based upon the loading of polymer-bound α-diazo-*β*-ketoesters **5**.

During our investigations of the amidation cleavage reaction, two interesting unexpected side reactions were discovered (Scheme 3). When R^1 was 3-NO_2−Ph, the major product obtained from the amidation cleavage reaction was isolated in 30% yield, but the spectral data did not agree with the presence of the nitro group in the cleavage product. Further analysis suggested that the nitro group in this compound **11** was reduced to the corresponding *N*-methylaminoindole **12** during the amidation cleavage reaction, and this was confirmed by ^{1}H, ^{13}C NMR, and mass spectrometry (presumably the amine/$AlMe_3$ reagent is the source of the methyl group). The corresponding 3-(3′-nitrophenyl)indole-2-carboxyic acid methyl ester **10** (entry 5) was obtained in 94% purity and 51% isolated yield when using the alternative transesterification cleavage reaction. Consequently, each of the subsequent nitro-functionalized indoles was cleaved from the resin as their corresponding esters **10** (entries 27 and 43).

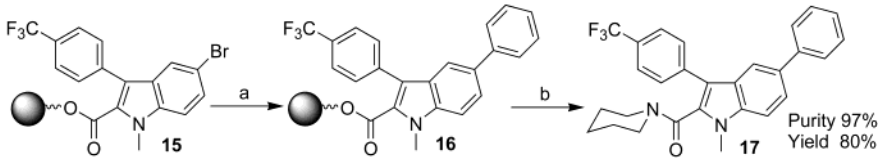
The acetamido group was also affected during the amidation cleavage reaction (Scheme 3). Extensive experimentation led to the conclusion that the acetamido group of indole **13** was converted into the corresponding amidine **14**, as confirmed by ^{1}H, ^{13}C NMR, and mass spectrometry. We note that in the original report for the conversion of esters to amides by Weinreb,[20] the acetamido group was tolerated under the relatively mild reaction conditions (40 °C), and this suggests that the use of higher reaction temperatures could potentially be of synthetic utility for the synthesis of amidines.[21] As a consequence, each of the amide or oxazoline-functionalized indoles (entries 9−10 and 12) was also cleaved by transesterification to give the corresponding esters **10**.

The final part of our study was the addition of extra building blocks onto the indole scaffold (Scheme 4). This was achieved by Suzuki coupling reaction of a bromo-functionalized polymer-bound indole. Here, 5-bromo indole **15** was treated with phenylboronic acid under Suzuki coupling conditions[11m] to give polymer-bound phenylated indole **16**, which was then cleaved by amidation to give the desired product **17** in excellent purity and yield.

Conclusion

In summary, we have demonstrated the solid-phase version of the Bischler indole synthesis using the N−H insertion

Scheme 4. Elaboration of polymer-bound indoles using a Suzuki coupling reaction.



(a) Phenylboronic acid (10 equiv), K_3PO_4 (10 equiv), Pd (dppf)Cl_2 (20 mol %), dioxane, 90 °C, 24 h. (b) Piperidine (10 equiv), $AlMe_3$ (5 equiv), toluene, 110 °C, 16 h.

reaction of *N*-alkylanilines into a polymer-bound rhodium carbenoid intermediate as the key step. Optimal conditions for the rhodium carbenoid insertion reaction and the acid-mediated cyclodehydration of resulting N−H insertion products into corresponding indoles has been established. This comprehensive study has given a great insight to the scope and limitations of this chemistry. The majority of the final products were obtained in good yield and excellent purity as either the indole-2-carboxamides or methyl indole-2-carboxylates using amidation or transesterification cleavage reactions, respectively. In addition, the scope of the preparation of more diverse indoles has been demonstrated by introducing additional substituents onto the indole scaffold using a Suzuki coupling reaction.

This research again highlights the use of polymer-bound α-diazo-β-ketoesters **5** as modular building blocks for the generation of molecular diversity. Studies involving the use of polymer-bound α-diazo-β-ketoesters for the preparation of other interesting heterocyclic scaffolds are currently under investigation in our laboratory and will be reported in due course.

Experimental Section

General Methods. Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Anhydrous toluene and dioxane were obtained from Aldrich in Sure Seal bottles. THF was distilled from sodium-benzophenone ketyl. The *N*-methylanilines were prepared from the corresponding anilines according to literature precedent[22] (see Supporting Information). The ion-exchange resins used in product purification, Dowex 50WX2-200 and Dowex 1X2-200, were washed with distilled water, acetone, MeOH, and CH_2Cl_2 prior to use. A batch of mixed-bed ion-exchange resin was prepared by mixing equal quantities of these acidic and basic resins. The filtration/workup cartridges were prepared by placing ∼1 cm^3 of Florisil and ∼2 cm^3 of the mixed bed resin in a 5-mL plastic syringe equipped with a polyethylene frit. All of the glassware used in the solid-phase synthesis was silanized by treating with sigmacote. Anhydrous TsOH solution (0.1−0.5 M) in toluene was prepared by azeotropic removal of water from toluene containing the corresponding quantity of TsOH·H_2O using a Dean−Stark apparatus. Flash chromatography was carried out using Merck silica gel 60 (230−400 mesh). Preparative TLC was carried out on Merck 60 F_{254} plates (0.5 or 1.0 mm) using ethyl acetate/hexanes or ethyl acetate/chloroform mixtures.

FT-IR spectra were recorded using a Thermo Nicolet AVATA 360 spectrometer equipped with a golden gate single reflection diamond ATR accessory. NMR spectra were recorded using either a Bruker DRX-500 or 600 spectrometer and calibrated using residual undeuterated solvent as an internal reference. Analytical reversed-phase HPLC was carried out using a Hitachi system: L-5000 LC controller, 655A variable wavelength UV monitor, 655A-12 liquid chromatograph, and D-2000 chromatointegrator. Conditions: Vydac 201SP column (5-μm RP C_{18}) 4.6 mm × 250 mm; acetonitrile/water isocratic 60:40 or 50:50; flow rate, 1 mL min^{-1}; detection, UV (λ = 254 nm); injection loop, 2 μL. High-resolution mass spectra (HRMS) were recorded at The Scripps Research Institute using MALDI-FTMS techniques.

4-(5-Hydroxypentyl)styrene (3). A 2-L three-necked reaction flask equipped with a reflux condenser and a dropping funnel was charged with 4-chlorobutanol **1** (99.8 g, 0.92 mol) and THF (800 mL), placed under an atmosphere of argon, and then cooled in an ice/salt bath. To this, isopropylmagnesium chloride (2.0 M in THF, 460 mL) was slowly added via dropping funnel over 1 h before warming the mixture to room temperature over 0.5 h. The flask was then immersed in an oil bath, the mixture was warmed to 40 °C for 1 h, the heat source was removed, and magnesium turnings (11.0 g, 0.46 mol) were slowly added. Next, 1,2-dibromoethane (∼1.0 mL) was added dropwise (10 min) in order to initiate the Grignard reaction, and the mixture was then heated to reflux for 1.5 h before the heat source was removed and a second portion of magnesium turnings (11.0 g, 0.46 mol) was added, followed by initiation with 1,2-dibromoethane (∼1.0 mL, dropwise) and heating to reflux for 1.5 h. Finally, a third portion of magnesium (11.0 g, 0.46 mol) was added, and the 1,2-dibromoethane (∼1.0 mL) initiation followed by reflux (1.5 h) process was repeated before cooling the mixture to room temperature.

A 3-L round-bottomed flask was charged with 4-vinylbenzyl chloride **2** (105.3 g, 0.69 mol) and THF (500 mL), purged with argon, and then cooled in an ice/salt bath. The Normant−Grignard reagent prepared above was added via cannula over 2 h, and the mixture was allowed to warm to room temperature and stirred overnight. The excess reagent was quenched by the careful addition of methanol (300 mL) before concentration of the mixture using a rotary evaporator. Hydrochloric acid (1 M, 1 L) and ether (500 mL) were added, and the layers were separated. The aqueous phase was extracted three times with ether (500 mL) and the organic phases were combined and washed twice with ammonium chloride (500 mL) and brine (500 mL) and dried with magnesium sulfate. Activated decolorizing charcoal was added, and the mixture was filtered through Celite and was concentrated under reduced pressure to give a yellow oil. The product was purified by flash chromatography using a

gradient elution (100% hexanes to 25% ethyl acetate/hexanes) to give 4-(5-hydroxypentyl)styrene **3** (49.5 g, 38%) as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.39 (quintet, J = 7.6 Hz, 2H), 1.59 (quintet, J = 7.6 Hz, 2H), 1.64 (quintet, J = 7.6 Hz, 2H), 2.61 (t, J = 7.6 Hz, 2H), 3.63 (t, J = 6.5 Hz, 2H), 5.18 (dd, J = 1.0, 11.0 Hz, 1H), 5.70 (dd, J = 1.0, 17.5 Hz, 1H), 6.68 (dd, J = 11.0, 17.5 Hz, 1H), 7.13 (d, J = 7.9 Hz, 2H), 7.32 (d, J = 8.3 Hz, 2H).

Hydroxypentyl *J*anda*J*el 4. Acacia gum (140 g) and sodium chloride (87 g) were dissolved in water (3.5 L) by warming to ~50 °C for 1 h. This mixture was filtered through Celite and added to a 4-L jacketed reaction kettle, and the kettle was warmed to ~50 °C and purged with argon. Meanwhile, a homogeneous solution of 4-(5-hydroxypentyl)-styrene **3** (49.5 g, 0.26 mol), 1,4-bis-(4-vinyl)phenoxybutane (10.7 g, 36.3 mmol), and styrene (179 mL, 1.56 mol) in chlorobenzene (200 mL) was prepared by gentle warming. Benzoyl peroxide (3.00 g, 12.4 mmol) was added to the monomer solution, and the mixture was then added to the reaction kettle containing the aqueous phase. The aqueous/organic suspension was then stirred at 350 rpm using an overhead stirrer and the reaction kettle was heated to 80 °C overnight. After cooling, the polymer was collected on a large sintered filter and washed with copious amounts of hot water followed by methanol. The polymer was then extracted in a Soxhlet (THF) extraction for 48 h, after which time it was collected by filtration and washed with ether and hexanes and dried. Sieving gave 117 g of the desired hydroxypentyl *J*anda*J*el resin **4** in the 100−200 mesh size. The hydroxyl loading of this resin **4** (~1.1 mmol/g) was estimated by DMT quantitation.[23]

Preparation of Polymer-Bound α-Diazo-β-ketoesters 5. A round-bottomed flask was charged with hydroxypentyl *J*anda*J*el **4** (5.0 g, ~5.5 mmol), a *tert*-butyl β-ketoester (~18 mmol), and toluene (70 mL), and the mixture was heated to reflux overnight. After cooling, the product was collected by filtration and washed with DMF, THF, ether, and hexanes. The polymer-bound β-ketoester prepared above was swollen in toluene (70 mL), and Et_3N (2.51 mL, 18.0 mmol) and dodecylbenzenesulfonyl azide (6.33 g, 18.0 mmol) were added. The vessel was wrapped in aluminum foil, and the mixture was shaken for 24 h. The product was washed with DMF, THF, Et_2O, and hexanes to give **5** as a free-flowing off-white powder: IR 2140 cm^{-1} (C═N═N); resin loading was estimated using elemental analysis for nitrogen.

General Procedure for the Rhodium-Catalyzed N−H Insertion Reaction (5 → 7). A carousel reaction tube was charged with α-diazo-β-ketoester resin **5** (400 mg, ~0.3 mmol) and *N*-alkylaniline **6** (2 mmol) and purged with argon, and toluene (3 mL) was added. This mixture was heated to 100 °C for 5 min, and a solution of rhodium octanoate (6.2 mg, 8 μmol) and *N*-alkylaniline **6** (2.0 mmol) in toluene (1 mL) was added. Nitrogen effervescence was observed and subsided after ~10 min. After heating for an additional 3 h, the resin was collected in a plastic syringe equipped with a polyethylene frit and washed several times with DMF, MeOH, THF, ether, hexane, and $CHCl_3$, then dried in vacuo to give α-arylamino-β-ketoester resin **7** as a yellow powder.

General Procedure for the Cyclization Reaction (7 → 8). A carousel reaction tube was charged with α-arylamino-β-ketoester resin **7** (400 mg, ~0.3 mmol) and purged with argon, and a 0.1, 0.25, or 0.5 M solution of *p*-toluenesulfonic acid in toluene (6 mL) was added (see Table 1). This mixture was heated to reflux for 6 h. After being cooled to room temperature, the resin was collected in a plastic syringe equipped with a polyethylene frit and washed several times with DMF, MeOH, THF, ether, hexane, and $CHCl_3$, then dried in vacuo to give indole resin **8** as a brown powder.

General Procedure for the Cleavage Reaction. Amidation (8 → 9). Piperidine (0.1 mL, 1 mmol) was added dropwise to a stirred solution of trimethylaluminum in toluene (2.0 M, 0.3 mL, 0.6 mmol) and toluene (0.5 mL) at 0 °C under argon. After being stirred for 10 min at 0 °C, the resulting solution was warmed to room temperature and then added dropwise to a stirred suspension of the polymer-bound indole **8** (150 mg, ~ 0.1 mmol) and toluene (2 mL) in a 6-mL vial under argon. The vial was then closed tightly with a Teflon disk lid, and the resulting suspension was heated to 110 °C for 18 h. After the mixture was cooled to room temperature, saturated $NaHCO_3$ (0.1 mL) and THF (1 mL) were slowly added, and the mixture was stirred for an additional 10 min. The reaction mixture was passed through a filtration/workup cartridge and further eluted with THF−$CHCl_3$ (20 mL, 1:1). Compound bearing amine functionality (Table 1, entry 8) was passed through a workup cartridge that contained only Florisil and a basic ion-exchange resin. The combined filtrate was concentrated under reduced pressure, and then the purity of crude product was estimated by HPLC. Purification of crude product by preparative TLC gave indole 2-carboxamide **9**.

Transesterification (8 → 10). A solution of NaOMe in MeOH (0.5 M, 0.5 mL, 0.25 mmol) was added to a stirred suspension of the resin-bound indole **8** (150 mg, ~ 0.1 mmol) and THF (2 mL) in a 6-mL vial at room temperature under argon. The vial was then closed tightly with a Teflon disk lid, and the resulting suspension was heated to 50 °C for 1 h, then cooled to room temperature. The reaction mixture was passed through an acidic ion-exchange resin (~2 cm^3) and further eluted with THF−$CHCl_3$ (20 mL, 1:1). The combined filtrate was concentrated under reduced pressure, and then the purity of crude product was estimated by HPLC. Purification of crude product by preparative TLC gave methyl indole 2-carboxylate **10**. For entries 5, 10, and 12, a conventional aqueous workup was performed. Saturated aqueous ammonium chloride (1 mL) was added to the reaction mixture, and the resulting mixture was stirred for an additional 10 min and filtered, and the resin was washed with CH_2Cl_2 (5 mL × 3) and water (5 mL × 3) alternately. The organic layer of the combined filtrate was collected, and the aqueous layer was extracted with CH_2Cl_2 (5 mL × 3). The combined organic extract was dried over $MgSO_4$ and evaporated under reduced pressure, and then the purity of crude product was estimated by HPLC. Purification of crude product by preparative TLC gave methyl indole-2-carboxylate **10**.

Procedure for the Suzuki coupling reaction (15 → 16). A 6-mL vial was charged with polymer-bound indole **15** (250

mg, 0.18 mmol), phenylboronic acid (244 mg, 2.0 mmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (33 mg, 0.04 mmol), and K_3PO_4 (425 mg, 2.0 mmol). The vial was evacuated and filled with argon. Dioxane (3 mL) was added, and the vial was then closed tightly with a Teflon disk lid. The resulting suspension was heated to 90 °C for 24 h with vigorous shaking. After being cooled to room temperature, the resin was collected in a plastic syringe equipped with a polyethylene frit and washed several times with DMF, DMF−H_2O (1:1), H_2O, MeOH, THF, ether, hexane, and $CHCl_3$, then dried in vacuo to give the phenylated indole resin **16** as a dark brown powder.

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Supporting Information Available. Experimental procedures for the preparation of *N*-methylanilines **6** and full characterization data for all compounds synthesized and spectra for *N*-methylaminoindole **12** and amidine-indole **14**. This material is available free of charge via the Internet http://pubs.acs.org.

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