Indole Resin: A Versatile New Support for the Solid-Phase Synthesis of Organic Molecules

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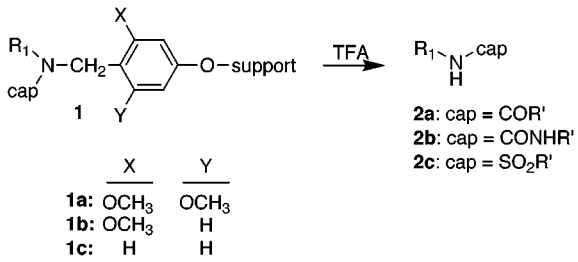
Combinatorial solid-phase chemistry is gaining momentum throughout the pharmaceutical industry as a powerful tool for preparing libraries of druglike organic molecules.[1] Recent advances have been reviewed.[2] In general terms, solid-phase chemistry can be broken down into three components: (1) the solid support, often a polystyrene resin; (2) the product molecule; and (3) the chemical tether (linker), which connects the two.

As the repertoire of solid-phase reactions expands to include the synthesis of more diverse targets, there is an increasing need for robust linkers that not only are cleaved in high yield under mild conditions but that also afford products bearing no extraneous functionality associated with resin attachment. One recent class of such "clean-break" linkers are those that are used to connect a nitrogen-containing product to a solid support via an N-(alkoxybenzyl) substitutent (**1a**,[3,4] **1b**,[5,6] and **1c**[5,6]). Acid-mediated cleavage



of these electron-rich tethers affords secondary amides (**2a**),[3−5] ureas (**2b**),[5] or sulfonamides (**2c**)[5,6] in which the resin attachment is replaced by a single proton. This method is conceptually very attractive, since it capitalizes on the vast diversity and availability of primary amines, carboxylic acids, sulfonyl chlorides, and isocyanates, and the products bear no evidence of resin attachment. In practice, however, these linkers appear to have significant limitations. We encountered difficulty reliably synthesizing the 4-formyl-3,5-dimethoxyphenol[7] used to prepare resin-bound amines **1a** (cap = H). Cleavage of the products from resins **1a**,[3,4] **1b**,[5] and **1c**[5,6] often requires ≥90% TFA. The synthesis of amides **2a** from the coupling of a carboxylic acid to the resin-bound amine **1a** (cap = H) was reported to be difficult due to the steric interference of the flanking methoxy groups on the linker.[3,4] The synthesis of sulfonamides from **1a** was not successful.[4] The synthesis of ureas from **1a** or **1b** has not been reported.

As part of our high-speed chemistry efforts, we were interested in developing a general solid-phase method for the preparation of nitrogenous products bearing no evidence of attachment to a solid support.[8] Herein, we report our initial results using the indole-terminated resin **5**. This resin is prepared in a facile three-step sequence and can be used to synthesize a wide range of secondary amides, sulfonamides, and ureas in high yield and under mild conditions.

The synthesis and general use of the indole resin **5** is described in Scheme 1. Indole-3-carboxaldehyde **3** was alkylated with ethyl bromoacetate in DMF at 80 °C, and after saponification with KOH in methanol (88% overall yield), the acid **4** was coupled to aminomethylated polystyrene[9] using *N*,*N*-diisopropylcarbodiimide (DIC), 1-hydroxybenzotriazole (HOBt), and $^{i}Pr_2EtN$ in DMF/CH_2Cl_2 (10% v/v) to afford indole resin **5**. The incorporation of **4** to the solid support was monitored using single-bead FT-IR (C═O absorption at 1665 cm^{-1}) and was judged complete based on a negative Kaiser test.[10] The elaboration of resin **5** into products **7**−**32** proceeded with the reductive amination of the carboxaldehyde of **5** using a primary amine and $(CH_3)_4NBH(OAc)_3$ in dichloroethane (16 h) followed by treatment with $NaBH_3CN$ in MeOH (6 h).[11] The resulting resin-bound secondary amines **6** were then treated with a variety of "nitrogen-capping groups" under standard conditions for solid-phase synthesis. For example, treatment of **6** with carboxylic acids (4 equiv) in the presence of bromotrispyrrolidinophosphonium hexafluorophosphate (PyBroP, 4 equiv) and $^{i}Pr_2NEt$ (8 equiv) in dichloromethane afforded resin-bound amides **7**−**19**,[12] treatment of **6** with a sulfonyl chloride (5 equiv), $^{i}Pr_2NEt$ (5 equiv), and DMAP (0.3 equiv) in 10% DMF/dichloroethane afforded sulfonamides **20**−**25**, treatment of **6** with an isocyanate (5 equiv) in dichloromethane afforded ureas **26**−**28**, and treatment of **6** with a chloroformate (4 equiv), $^{i}Pr_2NEt$ (8 equiv), and DMAP (0.3 equiv) in dichloromethane afforded carbamates **29** and **30**. Products were cleaved from the solid support using 50% TFA/CH_2Cl_2, typically using a 4 h exposure.[13] We have since discovered that 2−5% TFA/CH_2Cl_2 (4 h) is sufficient for most products.

Using the above synthetic route, we have prepared the examples listed in Table 1. In all instances, the crude products were obtained with a high degree of purity as

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(2) (a) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1997**, *53*, 5643−5678. (b) Balkenhohl, F.; von dem Bussche-Hünnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2288−2337. (c) Früchtel, J. S.; Jung, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 17−42.

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(4) Holmes, C. P.; Marquess, D. *New Linkers for Generating Substituted Amides and Ureas from Solid Supports*. Presented at the 213th National Meeting of the American Chemical Society, San Francisco, CA; American Chemical Society: Washington, DC, 1997; ORGN 383.

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(7) Landi, Jr., J. J.; Ramig, K. *Synth. Commun.* **1991**, *21*, 167−171.

(8) During the preparation of this paper, the synthesis of N-substituted amides using the Rink linker were reported: Garigipati, R. S. *Tetrahedron Lett.* **1997**, *38*, 6807−6810. Brown, E. G.; Nuss, J. M. *Tetrahedron Lett.* **1997**, *38*, 8457−8460.

(9) Aminomethyl polystyrene resin (1% cross-linked, 200−400 mesh) with a loading of 0.70−0.75 mequiv/g was purchased from Bachem and used without further treatment.

(10) Kaiser, E.; Colescott, R. L.; Bossinger, C. D.; Cook, P. I. *Anal. Biochem.* **1970**, *34*, 595−598.

(11) The use of sequential hydride reagents represents the standard reductive amination conditions used by our laboratory. These conditions are based on our observation that $(CH_3)_4NBH(OAc)_3$ alone is often insufficient for complete reduction, while $NaBH_3CN$ can afford impure products in unsatisfactory yield.

(12) Other acid coupling conditions: carboxylic acid (4 equiv), HOBt (8 equiv), DIC (8 equiv), and $^{i}Pr_2NEt$ (4 equiv) in 10% DMF/dichloroethane; carboxylic acid (4 equiv), phenyl dichlorophosphate (4 equiv), and triethylamine (8 equiv) in THF; carboxylic acid (5 equiv), TFFH (5 equiv), and $^{i}Pr_2NEt$ (5 equiv) in DMF.

(13) The cleavage of **7** in 50% TFA/CH_2Cl_2 at room temperature was complete in 30 min, as determined by HPLC analysis.

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Scheme 1

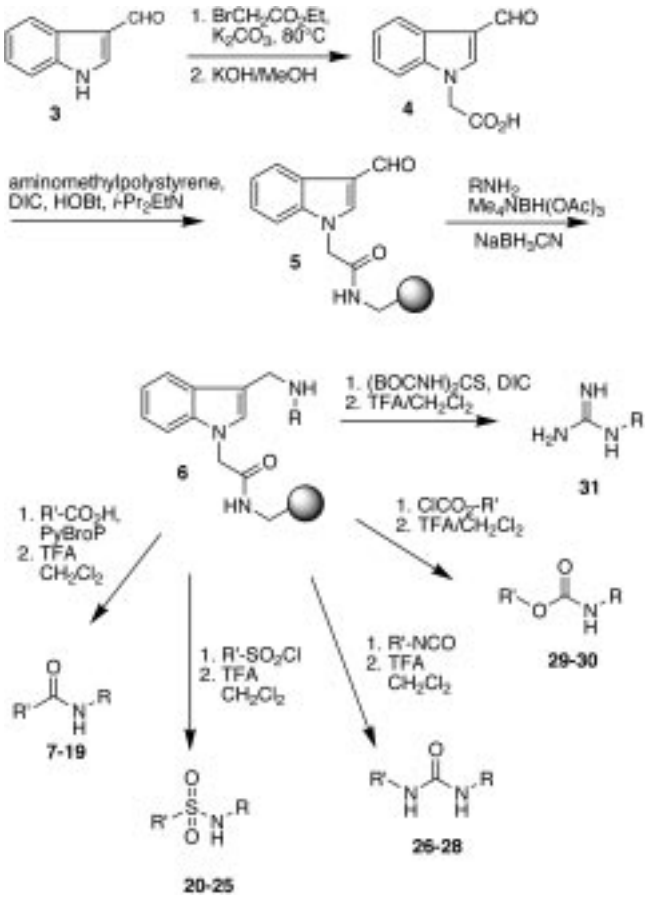


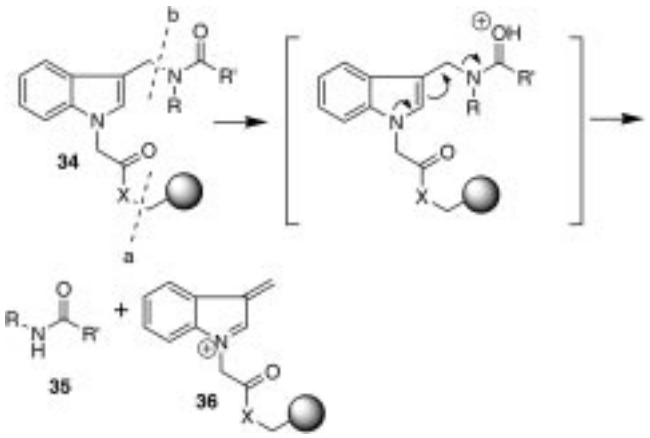
Table 1. Synthesis of Products R_1NHR_2 Using Indole Resin 5

no.	R_1	R_2	yield[a]
7	3,4-di-OMe-Ph$(CH_2)_2$	$COCH_3$	>99
8	2-Cl−PhCH_2	$COCH_3$	>99
9	3-pyridinylmethyl	$COCH_3$	97
10	2-thienylmethyl	$COCH_3$	100
11	2-pyrrolidinone-1-$(CH_2)_3$	$COCH_3$	89
12	Ph$CH_2C(CH_3)H$	$COCH_3$	83
13	1-adamantylmethyl	$COCH_3$	95
14	$CH_3O(CH_2)_3$	$COCH_3$	97
15	4-OMe-PhCH_2	$COCH_2NHFmoc$	>99
16	3,5-di-Me-4-OTBS−Ph	$COCH_2NHFmoc$	>99
17	3,5-di-Me-4-OTBS−Ph	COC_6H_{13}	95
18	PhCH_2	COC_6H_{13}	89
19	PhCH_2	COC_3H_7	91
20	Et	SO_2-*p*-tolyl	99
21	$Et_2N(CH_2)_3$	SO_2-*p*-tolyl	93
22	PhCH_2	SO_2Ph-4-OMe	96
23	PhCH_2	SO_2Ph-2,5-di-OMe	96
24	PhCH_2	SO_2-*p*-tolyl	99
25	3,5-di-Me-4-OTBS−Ph	SO_2-*p*-tolyl	>99
26	PhCH_2	$CONHC_3H_7$	88
27	PhCH_2	CONHPh	86
28	3,5-di-Me-4-OTBS−Ph	CONH-*o*-tolyl	>99
29	PhCH_2	CO_2Ph	59
30	PhCH_2	$CO_2C_3H_7$	80
31	4-OMe-PhCH_2	C=NH(NH_2)	96
32	3,5-di-Me-4-OTBS−Ph	H	>99
33	4-OMe-PhCH_2	H	0

[a] Isolated yields based on the loading of **5**. All compounds were base-line pure by proton NMR.

assessed by ^{1}H NMR. When impurities were present, they were minor and could be attributed to residual coupling reagents (HOBt, Et_3N−HCl) or unidentified aliphatic materials presumed to leach from the resin upon exposure to TFA. These contaminated products were purified by passing them through a short plug of silica gel. The final yields for amide, sulfonamide, and urea products were >85%, and often >90% overall, as determined from the loading of the indole aldehyde **5**.[14] Primary amines with α-branching reacted satisfactorily (**12**), as did the aniline examples (**16**, **17**, **25**, and **28**). The reaction of resin-bound amines with chloroformates was less successful, as our standard conditions afforded products in need of chromatography and in modest yield (**29** and **30**). The guanidine **31** was obtained in 96% yield by treating **6** with *N*,*N*′-bis-BOC-thiourea and DIC.[15] It is noteworthy that aniline **32** was released from the resin in excellent yield despite the absence of an activating R_2 capping group, while the analogous treatment of resin-bound benzylamine **6** (R = 4-OMePhCH_2) with up to 95% TFA afforded none of the uncapped product **33**.

Scheme 2



While the compounds listed in Table 1 were prepared using the indole linker coupled to an aminomethyl polystyrene support, our preliminary results indicate that the indole linker may be used with acid-labile resins (e.g., Wang, Rink, or Rink AM) without affecting the purity or yields of the amide products. A mechanism for product release is proposed in Scheme 2 using resin-bound amide **34** as the exemplar. In the case of aminomethyl polystyrene (X = NH), cleavage occurs at bond *b* via protonation of the amide and elimination of the product **35** from the electron-rich indole core. Although the use of Wang or Rink resin introduces an alternative site of acid lability (bond a), treatment of these resins with TFA in dichloromethane (5% for Rink, 50% for Wang) again induced cleavage exclusively at bond *b*, affording **35** in high yield with no evidence of indole-containing byproducts. The lack of indole impurities in the crude product **35** indicates that scission at bond *a* does not occur after **35** is eliminated. The high yields listed in Table 1 suggest that the resin-bound cation **36** does not react with those solution-phase products after they are released. No cation scavengers were used.

In summary, we have found the indole resin **5** to be an ideal support for preparing libraries of amides, ureas, sulfonamides, guanidines, carbamates, and aniline-containing products. We are currently exploring the performance of **5** with a wider range of chemistries. These results will be reported in due course.

Supporting Information Available: Experimental details and NMR spectral data for compounds **7**−**32** (39 pages).

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(14) The loading of **5** was determined using a "cleave and weigh" procedure: **5** was reductively aminated with *p*-methoxybenzylamine, acylated with acetic anhydride, and cleaved with 50% TFA/dichloromethane and the resulting acetamide quantified. The loading of **5** was calculated to reflect the amount of acetamide obtained and was typically between 0.5 and 0.7 mequiv/g.

(15) Robinson, S.; Roskamp, E. J. *Tetrahedron* **1997**, *53*, 6697−6705.