Pergamon

Tetrahedron Letters, Vol. 38, No. 46, pp. 7963-7966, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10140-X

The Solid Phase Synthesis of Tri-Substituted Indoles

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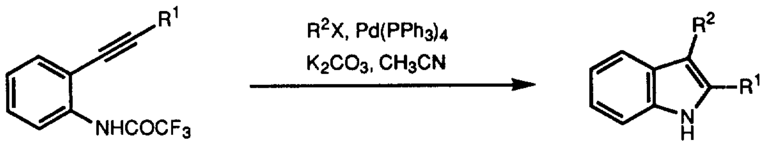
Abstract: The palladium-catalyzed solid phase synthesis of tri-substituted indoles is described. The synthesis incorporates three independently variable groups and is ideally suited for the preparation of combinatorial libraries. © 1997 Elsevier Science Ltd.

The solid phase synthesis of small organic molecules has recently become important because of the utility of this methodology for producing combinatorial libraries.[1] While the formation of amide bonds on a solid support has been optimized, other types of reactions have not been studied as extensively. Carbon-carbon bond formation and reactions in which a heterocycle is formed are of particular importance for the synthesis of small organic molecules used in drug discovery research. Palladium catalyzed processes have been used for both of the above reaction classes, and therefore appeared to be a fruitful area for extension to solid phase synthesis. Described below is the application of two Pd catalyzed reactions for the synthesis of tri-substituted indoles on a solid support.

Several solid phase syntheses of indoles have been reported recently, including a Fisher indole synthesis,[2] a synthesis utilizing an intramolecular Heck reaction,[3] and a synthesis using the palladium-catalyzed coupling of terminal alkynes.[4] The publication of the last paper prompted us to report our results.[5]

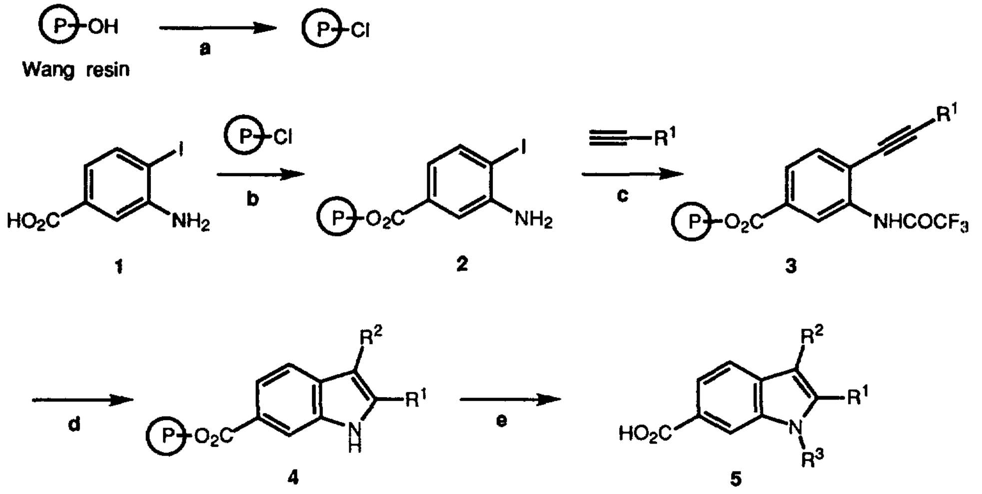
A combinatorial synthesis requires that at least two components of the product molecules be independently variable, so that all of the combinations of these components can be prepared. A synthesis with three independently variable components is preferable since greater diversity in structure can be produced in the resultant library. Thus, to prepare a combinatorial library of indoles with a high degree of potential diversity and wide utility for drug discovery using solid phase techniques, it was important to identify an indole synthesis in which three components could be independently varied. The solution phase synthesis of indoles reported by Arcadi and Cacchi[6] incorporates two components in an independent fashion through palladium-catalyzed processes (Scheme 1).

Scheme 1



The indoles prepared by this route can then be alkylated on nitrogen to incorporate a third component. By adapting this solution phase synthesis to a solid-supported synthesis, it is possible to prepare combinatorial libraries of indoles. The general synthesis of indoles with three variable components is outlined in Scheme 2.

Scheme 2

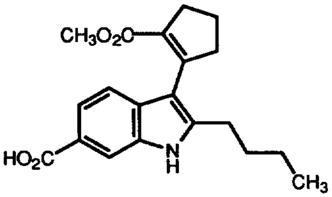


a: MsCl, LiCl, collidine, DMF, 18 h; **b:** Cs_2CO_3, DMF, 50° C, 24 h; **c:** i) $PdCl_2(PPh_3)_2$, CuI, Et_2NH, DMF, 2 h; ii) $(CF_3CO)_2O$, pyridine, CH_2Cl_2, 2 h; **d:** R^2OTf, $Pd(PPh_3)_4$, K_2CO_3, DMF, 24 h; **e:** i) R^3X, NaH, DMF, 4 h; ii) TFA, CH_2Cl_2, 2 h.

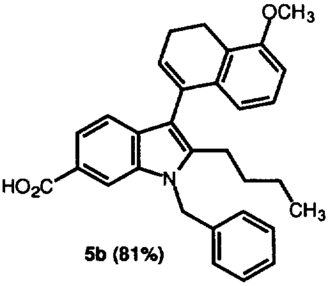
It was found that 3-amino-4-iodobenzoic acid could be directly attached to a modified Wang resin as the cesium salt without a protecting group on the nitrogen. Only Wang resin was used in this work. Thus, Wang resin was converted to chloro-Wang resin with MsCl, LiCl, and collidine in DMF. Benzoic acid **1**[7] was attached to the resin with Cs_2CO_3 in DMF at 50° C for 24 h to give resin **2** in 80-90% yield (loading 0.6 mmol/g). Coupling of a terminal alkyne according to the procedure of Sonogashira[8] and trifluoroacetylation gave resin **3**. If the nitrogen was trifluoroacetylated prior to coupling with an alkyne, compound **3** was not produced and only a 2-substituted indole was isolated. Cyclization of **3** to an indole with the incorporation of a vinyl group from a vinyl triflate (prepared from a ketone with NaH and $(CF_3SO_2)_2O$ according to Piers[9]) at the indole 3-position gave resin **4**. As described before,[6] K_2CO_3 is the optimal base for the cyclization reaction. It was expected that a soluble base would be needed for a solid phase reaction, but when Et_3N was used little product was obtained. Alkylation with NaH and an alkyl halide and treatment with TFA/CH_2Cl_2 yielded the product **5**. Again, the solid base (NaH) was optimal, but trace amounts of water may result in hydroxide generation.

Utilizing this general method four indoles (**5a**-**5d**) were prepared in the isolated and purified yields[10] indicated in Figure 1 below. Thus, 1-hexyne was coupled with resin **2** and cyclized in the presence of 2-carbomethoxy-1-cyclopentenyl triflate to give compound **5a**. Cyclization with 3,4-dihydro-5-methoxynaphthalenyl triflate and alkylation with benzyl bromide gave compound **5b**. Compounds **5c** and **5d** were prepared by coupling resin **2** with N-(4-methoxybenzoyl)-N-methylpropargyl amine and cyclization with the triflate derived from benzosuberone. Alkylation with ethyl bromoacetate gave **5d**.

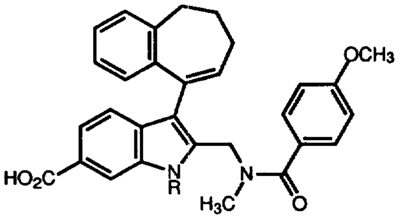
Figure 1



5a (65%)

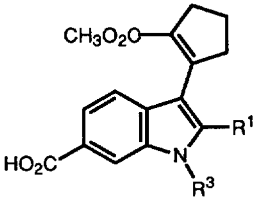


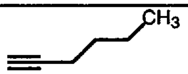
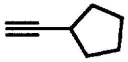
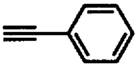
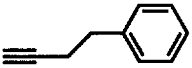
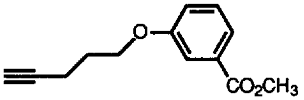
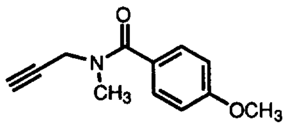
5b (81%)



5c: R = H (70%)
5d: R = CH_2CO_2Et (55%)

Table: Indoles Prepared from 2-Carbomethoxy-1-cyclopentenyl Triflate[11]



Entry	≡—R^1	Yields	
		Indoles (R^3=H)	Alkylation with R^3X[a]
1		34%	A (33%) B (55%)
2		75%	A (41%) B (38%)
3		60%	A (58%) B (71%)
4		60%	A (62%) B (67%)
5		68%	A (58%) B(40%)
6		76%	A (70%) B (73%)

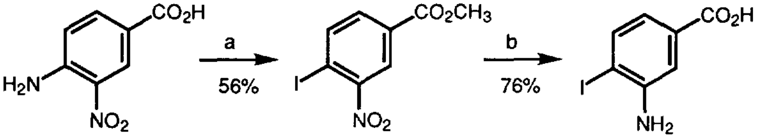
[a] R^3X: A: CH_3I; B: $BrCH_2CO_2Et$

A set of indoles was prepared from six terminal alkynes, 2-carbomethoxy-1-cyclopentenyl triflate, and two alkylating agents, as summarized in the Table. The compounds were prepared from resin **2** (100 mg resin per compound) to give 7 to 24 mg of product. Yields for the non-alkylated indoles (column 3) ranged from 34% to 76%, while yields for the alkylation step (column 4) ranged from 33% to 73%.

In summary, a solid phase synthesis of indoles with three independently variable components has been developed. A wide range of commercially available terminal alkynes can be used in the first step, and active alkylating agents, such as benzyl halides or bromoacetates are suitable for the third component. The vinyl triflates used to introduce the second component are not commercially available but are easily prepared in one step from ketones. Two of the components are introduced through mild, palladium-catalyzed reactions making this chemistry suitable for the production of combinatorial libraries.

REFERENCES AND NOTES

1. Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. *Tetrahedron* **1996**, *52*, 4527-4554.
2. Hutchins, S. M.; Chapman, K. T. *Tetrahedron Lett.* **1996**, *37*, 4869-4872.
3. Zhang, H.-C.; Maryanoff, B. E. *J. Org. Chem.* **1997**, *62*, 1804-1809.
4. Fagnola, M. C.; Candiani, I.; Visentin, G.; Cabri, W.; Zarini, F.; Mongelli, N.; Bedeschi, A. *Tetrahedron Lett.*, **1997**, 2307-2310.
5. A preliminary account was reported at the 213th ACS National Meeting, San Francisco, CA, April 13, 1997.
6. Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett.* **1992**, *33*, 3915-3918.
7. Compound **1** was prepared from 4-amino-3-nitrobenzoic acid in four steps in an overall yield of 42%:



a: i) $NaNO_2$, KI, HCl, 0 °C; ii) H_2SO_4, CH_3OH, reflux; **b**: i) $SnCl_2{\bullet}2H_2O$, EtOAc, reflux; ii) NaOH, CH_3OH.

8. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467-4470.
9. Piers, E.; and Tse, H. L. A. *Tetrahedron Lett.* **1984**, *25*, 3155-3158.
10. Compounds were characterized by MS, ^1H NMR, and HPLC.
11. The alkyne resins **3** were prepared on a 3 g scale: 3.0 g (1.8 mmol) of resin **2** was suspended in DMF (40 mL). Alkyne (9.0 mmol), Et_2NH (30 mL), $PdCl_2(PPh_3)_2$ (0.29 mmol), and CuI (0.525 mmol) were added and the mixture was stirred at r.t. for 2 h. The resin was filtered and washed with DMF and CH_2Cl_2. Trifluoroacetylation with TFAA (2.6 mL), pyridine (1.5 mL), and CH_2Cl_2 (50 mL) gave resin **3** (3.05-3.07 g). A 100 mg portion of each resin **3** was suspended in DMF (1 mL) and K_2CO_3 (70 mg) was added. 2-Carbomethoxy-1-cyclopentenyl triflate (55 mg) and DMF (1 mL) containing $Pd(PPh_3)_4$ (15 mg) were added. The mixture was stirred for 24 h at r.t., filtered, and washed to give resin **4**. The product was either cleaved with 50% TFA/CH_2Cl_2 to give non-alkylated indole or alkylated: to a suspension of resin **4** in DMF (1.5 mL) was added NaH (30 mg; 60% dispersion in oil). After 30 min, an alkyl halide (0.3 mmol) was added and stirring was continued for 4 h at r.t.. After filtration and washing, the products were cleaved from the resin with 50% TFA/CH_2Cl_2 (2 mL).

(*Received in USA* 22 *August* 1997; *revised* 4 *September* 1997; *accepted* 8 *September* 1997)