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Bartoli Indole Synthesis on Solid Supports

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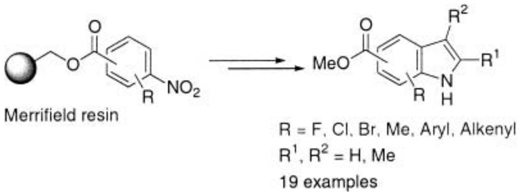
ABSTRACT



Bartoli indole synthesis has been performed for the first time on solid supports. Starting from Merrifield resin, immobilization of five nitro benzoic acids was performed. Addition of four different alkenyl Grignard reagents and basic cleavage leads to substituted methyl indole carboxylates in excellent purities. Features of this reaction are the stability of halide groups, ester moieties, and tolerance of *o,o′*-unsubstituted nitro resins. Heck and Sonogashira reactions are also possible with immobilized indoles.

The indole (from *indigo* and *oleum*) moiety is one of the most common heterocyclic structures found both in nature and in biologically active compounds.[1] The essential amino acid tryptophan,[2] the plant growth hormone heteroauxin,[3] and several groups of important alkaloids are indole derivatives.[4] It was shown that 3-methylindole (skatole) is produced with indole during pancreatic digestion or putrefactive decomposition of proteins, and hence both are found in the intestines and feces. Interest has centered on medicinal and biochemical aspects of indole chemistry. Serotonin,[5] which has been identified as a metabolite in neurochemistry, the psychotomimetic indoles psilocin[6] and psilocybin[7] isolated from mushrooms, the tranquillizer reserpine,[8] and the melanin pigments[9] are a few of the compounds that have been studied.

Some indole alkaloids exert considerable pharmacological activity, but quite different effects may be obtained even from alkaloids of one genus.

Therefore, indoles are a promising class of potentially useful pharmacologically active compounds and their synthesis in liquid phase and on solid supports[10] has found widespread application in organic chemistry. The most important examples are the reactions according to Fischer,[11] Bischler−Möhlau,[12] Martinet,[13] Hinsberg (oxindoles),[14] Reissert,[15] Nenitzescu,[16] Madelung−Tyson (cyclization of *N*-acyl-*o*-

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(1) (a) Sundberg, R. J. *The Chemistry of Indoles*; Academic Press: New York, 1970. (b) Sundberg, R. J. Pyrroles and Their Benzoderivatives: Synthesis and Applications. In *Comprehensive Heterocyclic Chemistry* ; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 4, pp 313−376 . (c) Sundberg, R. J. In *Best Synthetic Methods, Indoles*; Academic Press: New York, 1996; pp 7−11.

(2) Sandyk, R. *Int. J. Neurosci.* **1992**, *67*, 127.

(3) Armstrong, W. D.; Liu, Y.-S.; He, L.; Ekborg-Ott, K. H. *J. Agric. Food Chem.* **2002**, 473−476.

(4) Breitmaier, E. *Alkaloide*; Teubner Studienbücher Chemie: Stuttgart, 1997; pp 116−129.

(5) Kikuchi, C.; Nagaso, H.; Hiranuma, T.; Koyama, M. *J. Med. Chem.* **1999**, *42*, 533−535.

(6) Gathergood, N.; Scammells, P. J. *Org. Lett.* **2003**, *5*, 921−923.

(7) Nichols, D. E.; Frescas, S. *Synthesis* **1999**, *6*, 935−938.

(8) Mehta, G.; Reddy, D. S. *J. Chem. Soc., Perkin Trans. 1* **1998**, *14*, 2125−2126.

(9) De Marco, F.; Perluigi, M.; Marcante, M. L.; Coccia, R.; Foppoli, C.; Blarzino, C.; Rosei, M. A. *Biochem. Pharmacol.* **2002**, *64*, 1503−1512.

(10) Bräse, S.; Gil, C.; Knepper, K. *Bioorg. Med. Chem.* **2002**, *10*, 229−245.

(11) Fischer, E.; Jourdan, F. *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2241−2245.

(12) Bischler, A. *Chem. Ber*.**1892**, *25*, 2860.

(13) Guyot, A.; Martinet, J. *Compt. Rend.* **1913**, *156*, 1625.

(14) Hinsberg, O. *Chem. Ber.* **1988**, *21*, 110.

(15) Reissert, A. *Chem. Ber.* **1897**, *30*, 1030.

(16) Nenitzescu, C. D. *Bull. Soc. Chim. Romania* **1929**, *11***,** 37.

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toluidines),[17] Gassman (from *N*-halo anilines),[18] Leimgruber−Batcho (from *o*-nitrotoluenes and dimethylformamide acetals),[19] Baccolini (reaction by P−N fission of diazaphospholes),[20] and Bartoli,[21] as well as, e.g., Palladium-catalyzed alkynylation reactions and many others.[22,23] The solid-phase synthesis of indoles[24] and indolines, however, mainly focuses on two different approaches, namely, the palladium-catalyzed approaches[25] and the Fischer indole synthesis.[26] Some other examples have also been reported such as the reaction of supported anilines,[27] reactions using selenenyl reagents,[28] or the Nenitzescu reaction on solid supports.[29]

We were intrigued by the possibility of generating indoles on solid supports using the seldom-used Bartoli reaction since this reaction is particularly suitable for the synthesis of 7-substituted indoles.[30] In 1989, Bartoli et al. discovered that the reaction of 3 equiv of vinylmagnesium bromide with 2-substituted nitro arenes resulted in the formation of an indole moiety. With fewer equivalents of the Grignard reagent or by reaction of *o*,*o*′-unsubstituted nitro arenes, only traces of the indoles were isolated, if at all. The reaction mechanism is established, however, not in all details. While 1 equiv of the Grignard reduces the nitro group to a nitroso group, the second equivalent attacks the arene core, presumably via an electrocyclic reaction. Common side products are reduction products such as anilines and azo and azoxy compounds.

In this manuscript, we disclose the first solid-phase Bartoli reaction. A simple ester was chosen as the linker to investigate whether a fragile anchor might be suitable in principle. Moreover, this linker is selectively cleavable under basic conditions.[31] Other linkers might work even better. Simple polystyrene resin (Merrifield-type) was selected as an economical organic support.

Five different nitro benzoic acids **2**[32] were immobilized on Merrifield resin (chloromethylated polystyrene **1**, 1−2% cross-linked)[33] under standard conditions using cesium carbonate as a base.[34] The loadings were determined by elemental analysis and by cleavage with sodium methylate in methanol/THF.

The Bartoli reactions were performed on resins **3a**−**e** (1 g scale) at −40 °C in THF with four different alkenyl Grignard reagents **4**−**7**.[35] During the reaction, a color change into deep red was observed. Extension to allylmagnesium bromide failed at this point with all resins; only the reduced aniline derivatives were isolated after the cleavage.

Subsequently, the resins were washed with different polar and unpolar solvents (see Supporting Information).

The cleavage yielding the indoles **12**−**15** was carried out with 30% sodium methylate in methanol.[36] Most methyl indolecarboxylates were obtained in purities >80% without purification as judged by integration of the GC or ^{1}H NMR signals. The only exceptions are the reactions of the *o*,*o*′-unsubstituted nitroarene resin **3a** with propenyl Grignard reagents **5** and **6** (entries 2, 3). In this case, the reduced aniline derivatives were the main products. In general, 1-methylprop-1-enylmagnesium bromide (**7**) was the most efficient Grignard reagent.

Three features are remarkable for this overall transformation. First, in contrast to the literature precedence in liquid phase, *o*,*o*′-unsubstituted nitro arenes proved to be good substrates for the Bartoli reaction on solid support using certain Grignard reagents. The reduction to the corresponding anilines was only observed to a minor extent. The reductive coupling of the nitro arenes to form azo or azoxy benzenes was not detected at all. Second, the ester linker is compatible with the Grignard reagents used. A partial cleavage of the resin during the Bartoli reaction can be observed (10−40% as judged by elemental analysis, see Supporting Information) explaining the diminished yields. Only *ortho*-nitro benzoic

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(17) Madelung, W. *Chem. Ber*. **1912**, *45*, 1128.

(18) Gassman, P. G.; van Bergen, T. J. *J. Am. Chem. Soc.* **1973**, *95*, 590−591.

(19) (a) Moyer, M. P.; Shiurba, J. F.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 5106−5110. (b) Clark, R. D.; Repke, D. B. *Heterocycles* **1984**, *22*, 195−221.

(20) Baccolini, G.; Todesco. P. E. *J. Chem. Soc., Chem. Commun*. **1981**, 563.

(21) Bartoli, G.; Palmieri, G.; Bosco, M.; Dalpozzo, R. *Tetrahedron Lett.* **1989**, *30*, 2129−2132.

(22) (a) Dobson, D.; Todd, A.; Gilmore, J. *Synth. Commun.* **1991**, *21*, 611−617. (b) Kondo, Y.; Kojima, S.; Sakamoto, T. *Heterocycles* **1996**, *43*, 2741−2746.

(23) Recent examples: (a) Muchowski, J. M. *J. Heterocycl. Chem*. **2000**, *37*, 1293−1297. (b) Gil, G. S.; Groth, U. M. *J. Am. Chem. Soc*. **2000**, *122*, 6789−6790. (c) Edmondson, S. D.; Mastracchio, A.; Parmee, E. R. *Org. Lett.* **2000**, *2*, 1109−1112. (d) Brown, J. A. *Tetrahedron Lett*. **2000**, *41*, 1623−1626. (e) Ketcha, D. M.; Wilson, L. J.; Portlock, D. E. *Tetrahedron Lett*. **2000**, *41*, 6253−6258. (f) Zhang, H.-C.; Ye, H.; Moretto, A. F.; Brumfield, K. K.; Maryanoff, B. E. *Org. Lett.* **2000**, *2*, 89−92. (g) Takeda, A.; Kamijo, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 5662−5663. (h) Tokuyama, H.; Kaburagi, Y.; Chen, X.; Fukuyama, T. *Synthesis* **2000**, 429−434. (i) Rainier, J. D.; Kennedy, A. R. *J. Org. Chem.* **2000**, *65*, 6213−6216. (j) Toczko, M. A.; Heathcock, C. H. *J. Org. Chem*. **2000**, *65*, 2642−2645. (k) Iyengar, R.; Schildknegt, K.; Aube, J. *Org. Lett*. **2000**, *2*, 1625−1628.

(24) Knepper, K.; Ziegert, R. E.; Bräse, S. *PharmaChem*. **2003**, *6*, 8−11.

(25) (a) Smith, A. L.; Stevenson, G. I.; Swain, C. J.; Castro, J. L. *Tetrahedron Lett.* **1998**, *39*, 8317−8320. (b) Wu, T. Y. H.; Ding, S.; Gray, N. S.; Schultz, P. G. *Org. Lett*. **2001**, *3*, 3827−3830. (c) Yamazki, K.; Kondo, Y. *J. Comb. Chem*. **2002**, *4*, 191−192.

(26) (a) Hutchins, S. M.; Chapman, K. T. *Tetrahedron Lett.* **1996**, *37*, 4869−4872. (b) Cheng, Y.; Chapman, K. T. *Tetrahedron Lett.* **1997**, *38*, 1497−1500. (c) Cooper, L. C.; Chicchi, G. G.; Dinnell, K.; Elliott, J. M.; Hollingworth, G. J.; Kurtz, M. M.; Locker, K. L.; Morrison, D.; Shaw, D. E.; Tsao, K. L.; Watt, A. P.; Williams, A. R.; Swain, C. J. *Bioorg. Med. Chem. Lett*. **2001**, *11*, 1233−1236. (d) Tanaka, H.; Ohno, H.; Kawamura, K.; Ohtake A.; Nagase, H.; Takahashi, T. *Org. Lett.* **2003**, *5*, 1159−1162.

(27) Lee, S. H.; Clapham, B.; Koch, G.; Zimmermann, J.; Janda, K. D. *J. Comb. Chem*. **2003**, *5*, 188−196.

(28) Nicolaou, K. C.; Roecker, A. J.; Hughes, R.; van Summeren, R.; Pfefferkorn, J. A.; Winssinger, N. *Bioorg. Med. Chem*. **2003**, *11*, 465−476.

(29) Ketcha, D. M.; Wilson, L. J.; Portlock, D. E. *Tetrahedron Lett.* **2000**, *41*, 6253−6257.

(30) (a) Bo, M.; Dalpozzo, R.; Bartoli, G.; Palmieri, G.; Petrini, M. *J. Chem. Soc., Perkin Trans. 2* **1991**, 657−662. (b) Dobbs, A. P.; Voyle, M.; Whittall, N. *Synlett* **1999**, 1594−1596. (c) Pirrung, M. C.; Wedel, M.; Zhao, Y. *Synlett* **2002**, 143. (d) For a review: Ricci, A.; Fochi, M. *Angew Chem., Int. Ed*. **2003**, *42*, 1444−1446.

(31) Dahmen, S.; Bräse, S. In *Handbook of Combinatorial Chemistry*; Nicolaou, K. C., Hanko, R. Hartwig, W., Eds.; VCH: Weinheim, 2002; Chapter 4.

(32) *ortho*-Nitro benzoic esters failed to give indoles due to premature cleavage from the solid support.

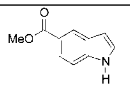
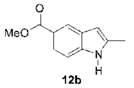
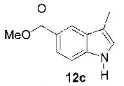
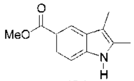
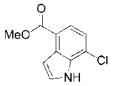
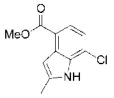
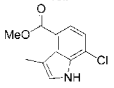
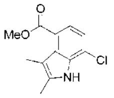
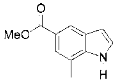
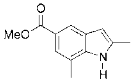
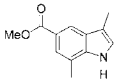
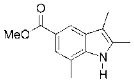
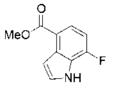
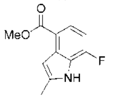
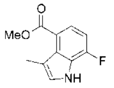
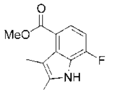
(33) Merrifield resin (0.93 mmol/g) was obtained from Polymer Laboratories (UK).

(34) All new nonpolymeric compounds were characterized by NMR, IR, MS, and HRMS. The purity was determined using GC, GC-MS, and NMR techniques. Polymeric compounds were characterized using IR and elemental analysis (CHN) (see Supporting Information).

(35) Grignard reagents are commercially available from Aldrich.

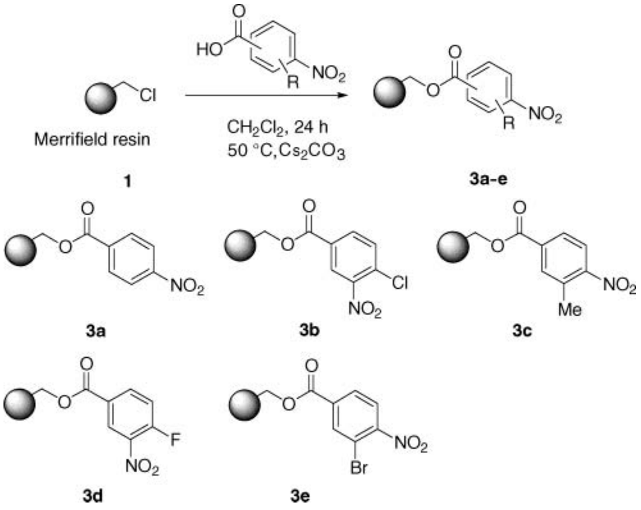
(36) Cleavage was quantitative as judged by elemental analysis of the remaining resin.

Table 1. Methyl Indolecarboxylates Prepared

entry	nitro arene resin	grignard reagent	indole	purity (%)[a]	yield (%)[b]
1	**3a**	**4**	 **12a**	82	15
2	**3a**	**5**	 **12b**	14[c]	28[c,d]
3	**3a**	**6**	 **12c**	16[c]	32[c,d]
4	**3a**	**7**	 **12d**	88	13
5	**3b**	**4**	 **13a**	94	15
6	**3b**	**5**	 **13b**	84	19
7	**3b**	**6**	 **13c**	98	11
8	**3b**	**7**	 **13d**	96	37
9	**3c**	**4**	 **14a**	79	17
10	**3c**	**5**	 **14b**	85	12
11	**3c**	**6**	 **14c**	81	12
12	**3c**	**7**	 **14d**	90	13
13	**3d**	**4**	 **15a**	80	18
14	**3d**	**5**	 **15b**	71	19
15	**3d**	**6**	 **15c**	81	20
16	**3d**	**7**	 **15d**	97	14

[a] Purity of the crude material as determined by GC and/or ^{1}H NMR. [b] Isolated yield of purified material over three steps based on the loading of the Merrifield resin used (see Supporting Information). [c] Main products are the reduced anilines. [d] Combined yields of products.

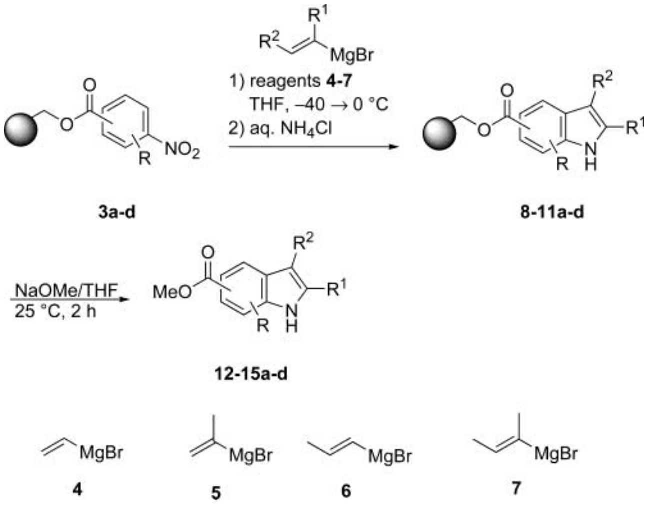
Scheme 1. Attachment of Nitro Benzoic Acids to Merrifield Resin



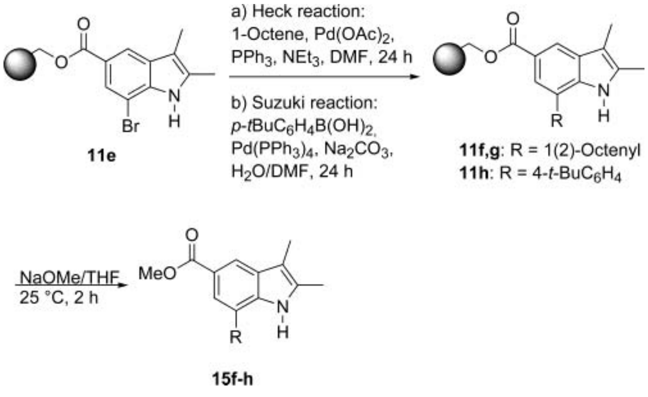
esters failed to give indoles due to premature cleavage from the solid support. Finally, this reaction can also be conducted on halogen-substituted nitro arenes, which typically undergo nucleophilic substitution if the halide is fluoride or chloride.[37]

To demonstrate an application of halogen-substituted indoles, both a Heck and a Suzuki reaction were performed on solid supports.[38a] As a result, reaction of the resin **11e**, prepared from resin **3e** and Grignard reagent **7**, with 1-octene under improved Heck conditions (Pd(OAc)$_2$, PPh$_3$, NEt$_3$, DMF, 24 h, 105 °C) provided after cleavage the alkenylated indoles **15f**,**g** as a mixture of the two regio isomers ((*E*)-1-octenyl and 2-octenyl)[38b] in a 1:1 ratio in good overall purities (together 96%) and 18% overall yield. Similarly, the Suzuki reaction of the resin **11e** with 4-*t*-butyl phenylboronic acid yielded the aryl-substituted resin **11h**. Cleavage yielded the indole **15h** in 88% purity and 15% overall yield (Scheme 3).

Scheme 2. Bartoli Reactions on a Solid Support



Scheme 3. Heck and Suzuki Reaction on a Bartoli Product



In conclusion, the first solid-phase synthesis of indoles using the Bartoli reaction starting from readily available compounds is presented. The products were obtained in high purities and moderate overall yields. Palladium-catalyzed reactions have been demonstrated on immobilized indoles. The presented work substantially extends the chemical transformations to be carried out on solid supports to give indoles in which three substituents can be varied.

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Supporting Information Available: Experimental procedures and characterizations for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(37) (a) Review: Ivachtchenko, A.; Sepetov, N. *Chim. Oggi* **2000**, *18*, 19−21. (b) Examples: Lee, J.; Gauthier, D.; Rivero, R. A. *J. Org. Chem.* **1999**, *64*, 3060−3065.

(38) (a) Bräse, S.; Kirchhoff, J. H.; Köbberling, J. *Tetrahedron* **2003**, *59*, 885−939. (b) Bräse, S.; de Meijere, A. In *Metal-catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998.