Reports

A Traceless Approach for the Solid-Phase Parallel Synthesis of Trisubstituted Oxindoles

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Solid-phase organic synthesis is a powerful tool for the preparation of small organic compounds to accelerate the drug discovery process.[1] Solid-phase heterocyclic compounds have received special attention because of their high degree of structural diversity and biologically interesting properties.[2] As a result, an increasing range and number of pharmaceutically useful heterocyclic compounds have been prepared recently using solid-phase methodology.[3] Oxindoles are interesting synthetic targets because of their various biological activities such as growth hormone secretagogues,[4] CDKs inhibitors,[5] anticancer compounds,[6] and AChE and BChE inhibitors.[7] There are many methods that have been developed for the synthesis of oxindoles both in solution phase and on solid phase, such as derivatization of other heterocycles,[8] cyclization of *o*-aminophenylacetic acid derivatives,[9] reduction of isatins,[10] Friedel−Crafts reaction (Stolle synthesis),[11] radical cyclizations,[12] intramolecular Heck reactions,[13] and Pummerer cyclizations.[14] These methods are very useful for the construction of the oxindoles; however, Stolle syntheses are of limited scope because of the harshly acidic conditions required, while many of the other methods are limited by the types of oxindoles that may be prepared because of the specifically functionalized precursors required or because the starting materials are not available conveniently. The Gassman oxindole synthesis,[15] which proceeds from a substituted aniline and ethyl (methylthio) acetate via chlorination of the sulfide and subsequent treatment with an arylamine and base such as triethylamine, is one of the most generally useful methods in terms of scope, starting material availability, brevity, and reproducibility.

As part of our ongoing efforts directed toward the solid-phase synthesis of heterocyclic compounds and the generation of combinatorial libraries of organic compounds,[16] herein, we wish to report an efficient traceless approach for the solid-phase synthesis of oxindoles via the Gassman oxindole synthesis. The parallel synthesis of oxindoles was carried out on the solid phase using the "tea-bag" methodology.[17] The reaction sequence is illustrated in Scheme 1.

Mercaptomethyl resin **1** was reacted with ethyl bromoacetate **2** in the presence of Et_3N in DCM to afford resin-bound compound **3**, which was reacted with an aniline **4** and *tert*-butyl hypochlorite (*t*-BuOCl) at −78 °C for 7 h and then treated with Et_3N at −78 °C for 7 h, followed by treatment with a 25% methanol solution of HCl at room temperature for 15 h to afford resin-bound oxindole **5.** To increase diversity around the oxindole template, the conversion of **5** to **7** was accomplished by oxidation of the sulfur link of **5** with *m*-chlorobenzoperoxoic acid (*m*-CPBA). Alkylation of **7** was examined, and the conversion of **7** into the corresponding 3-alkyl oxindole **8** was accomplished by treatment with reactive alkyl halides, such as allyl bromide, and benzyl bromides in the presence of K_2CO_3. Methylation of the 1-position of resin-bound oxindole **8** was achieved by reaction with CH_3I in the presence of NaH. The desired product oxindoles **6**, **9**, and **11** were cleaved from the resin by treatment with SmI_2 at room temperature. The oxindoles afforded are summarized in Table 1. All products were characterized by ^{1}H NMR, ^{13}C NMR, and LC-MS.

From these results a broad range of substituted anilines, which extends from mildly donating to strongly electron withdrawing, could be used as building blocks to synthesize oxindoles. When strongly electron-donating substituents on aniline, such as di- or trimethoxyaniline, were used, the result was unsatisfactory. While the starting aniline was meta-substituted, two isomers, 4-substituted and 6-substitued oxindoles, would theoretically be formed.[15] In fact, when the 3-bromoaniline (**4g**) was used as starting material, two isomers, 4-bromo-oxindole and 6-bromo-oxindole, were produced in a ratio of about 4:3, as determined from the ^{1}H NMR data. Selective alkylation of 3-position of oxindoles was achieved using a weak base K_2CO_3. Methylation of 1-position of oxindoles was accomplished using NaH. When a low-reactive alkyl halide was used as an alkylation reagent, such as bromoethane, no alkylated oxindole product **9** was found by LC-MS.

In summary, we have successfully developed an efficient traceless solid-phase approach to trisubstituted oxindoles from aromatic amines and alkyl halides. Mercaptomethyl resin **1** was reacted with ethyl bromoacetate **2** to afford resin-bound compound **3,** which was reacted with a substituted aniline to afford resin-bound oxindole **5** via the Gassman oxindole synthesis. Selective alkylation of the 1- and 3-positions of oxindoles was achieved by using different bases, such as K_2CO_3 and NaH. The resin-bound oxindoles

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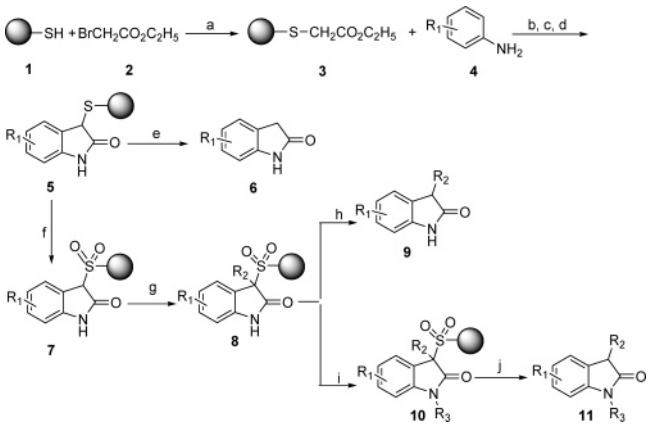
Scheme 1. Solid-Phase Synthesis of Trisubstituted Oxindoles[a]



[a] Reagents and conditions: (a) Et_3N (10 equiv, 6 mmol), DCM, roo, temp, 24 h, repeat; (b) *t*-BuOCl (10 equiv, 6 mmol), DCM, −78 °C, 7 h; (c) Et_3N (10 equiv, 6 mmol), −78 °C, 7 h; (d) 25% HCl in MeOH (10 mL), room temp, DCM, 15 h; (e) SmI_2 (5 equiv, 0.1 M), THF, room temp, 3 h; (f) *m*-CPBA (6.67 equiv, 4 mmol), DCM, room temp, 45 min; (g) R_2X (10 equiv, 0.15 M), K_2CO_3 (10 equiv), DMF, 24 h; (h) SmI_2 (5 equiv, 0.1 M), THF, room temp, 3 h; (i) R_3X (10 equiv, 0.15 M), NaH (10 equiv), THF, room temp, 40 h; (j) SmI_2 (5 equiv, 0.1 M), THF, room temp, 3 h.

Table 1. Product Oxindoles from Mercaptomethyl Resin

product	R_1	R_2	R_3	yield[a]	purity
6a	H	H	H	57%	93%[b]
6b	7-CH_3	H	H	51%	92%[b]
6c	5-CH_3	H	H	34%	91%[b]
6d	5-CF3	H	H	69%	95%[b]
6e	5-Br	H	H	66%	96%[b]
6f	5-F	H	H	60%	96%[b]
6g[d]	4-Br or 6-Br	H	H	68%	94%[b]
6h	5-$CO_2C_2H_5$	H	H	70%	96%[b]
6i	4-Cl, 7-CH_3	H	H	65%	95%[b]
6j	5, 7-Cl, Cl	H	H	71%	96%[b]
9a	5-Br	$CH_2CH{=}CH_2$	H	43%	>95%[c]
9b	5-F	$PhCH_2$	H	38%	>95%[c]
9c	5-$CO_2C_2H_5$	*p*-BrPhCH_2	H	44%	>95%[c]
9d	5, 7-Cl, Cl	$PhCH_2$	H	41%	>95%[c]
11a	5-F	$CH_2CH{=}CH_2$	CH_3	21%	>95%[c]
11b	5-CF_3	$PhCH_2$	CH_3	23%	>95%[c]

[a] Percent yields are based on the weight of isolated products and are relative to the initial loading of the resin. [b] HPLC purity of crude product (λ = 254 nm). [c] HPLC purity of isolated product purified by flash chromatography (λ = 254 nm). [d] **6g** is a mixture of 4-bromo-oxindole and 6-bromo-oxindole with a ratio of about 4:3.

5, **8**, and **10** were cleaved by SmI_2 to afford the desired oxindole products.

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Supporting Information Available. Experimental procedures, ^1H and ^{13}C NMR spectral data for **6a**, **6b**, **6d**, **6g**, **6i**, **9c**, **9d**, **11a**, and **11b**, and LC-MS data for **6d**, **9c**, **9d**, **11a**, and **11b**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) Sadaghiani, A. M.; Verhelst, S. H. L.; Bogyo, M. *J. Comb. Chem.* **2006**, *8*, 802. (b) Johansson, P.-O.; Chen, Y.; Belfrage, A. K.; Blackman, M. J.; Kvarnström, I.; Jansson, K.; Vrang, L.; Hamelink, E.; Hallberg, A.; Rosenquist, Å.; Samuelsson, B. *J. Med. Chem.* **2004**, *47*, 3353. (c) Duan, D.; Lewin, N. E.; Sigano, D. M.; Blumberg, P. M.; Marquez, V. E. *J. Med. Chem.* **2004**, *47*, 3248. (d) Kromann, H.; Krikstolaityte, S.; Andersen, A. J.; Andersen, K.; Krogsgaard-Larsen, P.; Jaroszewski, J. W.; Egebjerg, J.; Strømgaard, K. *J. Med. Chem.* **2002**, *45*, 5745. (e) Houghten, R. A.; Pinilla, C.; Appel, J. R.; Blondelle, S. E.; Dooley, C. T.; Eichler, J.;Nefzi, A.; Ostresh, J. M. *J. Med. Chem.* **1999**, *42*, 3743. (f) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555.

(2) Franzén, R. G. *J. Comb. Chem.* **2000**, *2*, 195.

(3) (a) Krchňák, V.; Holladay, M. W. *Chem. Rev.* **2002**, *102*, 61. (b) *Solid-Phase Organic Synthesis*; Czarnik, A. W., Ed.; John Wiley & Sons Ltd.: New York, 2001. (c) *Solid-Phase Organic Synthesis*; Burgess, K., Ed.; John Wiley & Sons Ltd.: New York, 2000.

(4) (a) Tokunaga, T.; Hume, W. E.; Nagamine, J.; Kawamura, T.; Taiji, M.; Nagata, R. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1789. (b) Tokunaga, T.; Hume, W. E.; Umezome, T.; Okazaki, K.; Ueki, Y.; Kumagai, K.; Hourai, S.; Nagamine, J.; Seki, H.; Taiji, M.; Noguchi, H.; Nagata, R. *J. Med. Chem.* **2001**, *44*, 4641.

(5) (a) Luk, K.-C.; Simcox, M. E.; Schutt, A.; Rowan, K.; Thompson, T.; Chen, Y.; Kammlott, U.; DePinto, W.; Dunten, P.; Dermatakis, A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 913. (b) Woodard, C. L.; Li, Z.; Kathcart, A. K.; Terrell, J.; Gerena, L.; Lopez-Sanchez, M.; Kyle, D. E.; Bhattacharjee, A. K.; Nichols, D. A.; Ellis, W.; Prigge, S. T.; Geyer, J. A.; Waters, N. C. *J. Med. Chem.* **2003**, *46*, 3877. (c) Bramson, H. N.; Corona, J.; Davis, S. T.; Dickerson, S. H.; Edelstein, M.; Frye, S. V.; Gampe, R. T., Jr.; Harris, P. A.; Hassell, A.; Holmes, W. D.; Hunter, R. N.; Lackey, K. E.; Lovejoy, B.; Luzzio, M. J.; Montana, V.; Rocque, W. J.; Rusnak, D.; Shewchuk, L.; Veal, J. M.; Walker, D. H.; Kuyper, L. F. *J. Med. Chem.* **2001**, *44*, 4339.

(6) (a) Zhu, G.-D.; Gandhi, V. B.; Gong, J.-c.; Luo, Y.; Liu, X.-s.; Shi, Y.; Guan, R.; Magnone, S. R.; Klinghofer, V.; Johnson, E. F.; Bouska, J.; Shoemaker, A.; Oleksijew, A.; Jarvis, K.; Park, C.; Jong, R.-D.; Oltersdorf, T.; Li, Q.; Rosenberg, S. H.; Giranda, V. L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3424. (b) Natarajan, A.; Guo, Y.; Harbinski, F.; Fan, Y.-H.; Chen, H.; Luus, L.; Diercks, J.; Aktas, H.; Chorev, M.; Halperin, J. A. *J. Med. Chem.* **2004**, *47*, 4979.

(7) (a) Yu, Q.-S.; Holloway, H. W.; Flippen-Anderson, J. L.; Hoffman, B.; Brossi, A.; Greig, N. H. *J. Med. Chem.* **2001**, *44*, 4062. (b) Shaw, K. T. Y.; Utsuki, T.; Rogers, J.; Yu, Q.-S.; Sambamurti, K.; Brossi, A.; Ge, Y.-W.; Lahiri, D. K.; Greig, N. H. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 7605.

(8) Sundberg, R. J. *Indoles*; Academic Press: London, 1996; pp 17, 152−154.

(9) (a) Hardegger, E.; Corrodi, H. *Helv. Chim. Acta* **1956**, *39*, 514. (b) Corrodi, H.; Romeo, H.; Hardegger, E. *Helv. Chim. Acta* **1955**, *38*, 463.

(10) Crestini, C.; Saladino, R. *Synth. Commun.* **1994**, *24*, 2835.

(11) (a) Beckett, A. H.; Daisley, R. W.; Walker, J. *Tetrahedron* **1968**, *24*, 6093. (b) Sumpter, W. C. *Chem. Rev.* **1945**, *37*, 443.

(12) (a) Cabri, W.; Candiani, I.; Colombo, M.; Franzoi, L.; Bedeschi, A. *Tetrahedron Lett.* **1995**, *36*, 949. (b) Jones, K.; Wilkinson, J.; Ewin, R. *Tetrahedron Lett.* **1994**, *35*, 7673. (c) Jones, K.; McCarthy, C. *Tetrahedron Lett.* **1989**, *30*, 2657. (d) Bowman, W. R.; Heaney, H.; Jordan, B. M. *Tetrahedron Lett.* **1988**, *29*, 6657.

(13) (a) Hennessy, E. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 12084. (b) Arumugam, V.; Routledge, A.; Abell, C.; Balasubramanian, S. *Tetrahedron Lett.* **1997**, *38*, 6473. (c) Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* ***1*987**, *52*, 4130. (d) Mori, M.; Ban, Y. *Tetrahedron Lett.* **1976**, *17*, 1807.

(14) (a) McAllister, L. A.; Turner, K. L.; Brand, S.; Stefaniak, M.; Procter, D. J. *J. Org. Chem.* **2006**, *71*, 6497. (b) McAllister, L. A.; McCormick, R. A.; Brand, S.; Procter, D. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 452. (c) McAllister, L. A.; Brand, S.; de Gentile, R.; Procter, D. J. *Chem. Commun.* **2003**, 2380. (d) Padwa, A.; Kuethe, J. T. *J. Org. Chem.* **1998**, *63*, 4256. (e) Kuethe, J. T.; Cochran, J. E.; Padwa, A. *J. Org. Chem.* **1995**, *60*, 7082.

(15) (a) Gassman, P. G.; Gruetzmacher, G.; van Bergen, T. J. *J. Am. Chem. Soc*. **1974**, *96*, 5512. (b) Gassman, P. G.; van Bergen, T. J. *J. Am. Chem. Soc.* **1974**, *96*, 5508. (c) Gassman, P. G.; Gruetzmacher, G.; van Bergen, T. J. *J. Am. Chem. Soc*. **1973**, *95*, 6508.

(16) (a) Yu, Y.; Ostresh, J. M.; Houghten, R. A. *J. Comb. Chem.* **2004**, *6*, 83. (b) Nefzi, A.; Ostresh, J. M.; Yu, Y.; Houghten, R. A. *J. Org. Chem*. **2004**, *69*, 3603. (c) Yu, Y.; Ostresh, J. M.; Houghten, R. A. *J. Org. Chem*. **2002**, *67*, 3138.

(17) Houghten, R. A. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 5131.

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