ORGANIC LETTERS

2009
Vol. 11, No. 20
4485−4487

Protecting-Group-Free Synthesis of 3-*tert*-Prenylated Oxindoles: Contiguous All-Carbon Quaternary Centers via Tertiary Neopentyl Substitution

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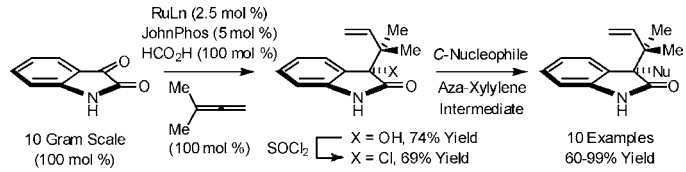
Received August 10, 2009

ABSTRACT



Ruthenium-catalyzed *tert*-prenylation of isatin 1 occurs efficiently in the absence of *N*-protecting groups under the conditions of C−C bond-forming transfer hydrogenation employing 1,1-dimethylallene as the prenyl donor. The prenylated adduct, 3-hydroxy-3-*tert*-prenyl-oxindole 2, is converted to the tertiary neopentyl chloride 3, which participates in nucleophilic substitution by way of an aza-*o*-xylylene intermediate to furnish adducts 4a−4i. Through tertiary neopentyl substitution, two contiguous all-carbon quaternary centers are established.

Prenylated indole alkaloids have attracted attention due to their remarkable biological effects and challenging structural features.[1] Those incorporating *tert*-prenyl moieties at the 2- or 3-position include the brevianamides, austamides, paraherquamides, marcfortines, echinulins, aspergamides, norgeamides, avrainvillamides, stephacidins, notamides, and roquefortines, as well as the amauromine, ardeemin, and flustramine families of natural products. The construction of indole alkaloids that incorporate a 3-*tert*-prenyl moiety requires construction of two contiguous all-carbon quaternary centers. Typically, this substructure is installed through the reaction of bis-*N*-protected tryptophan derivatives with *N*-(phenylseleno)phthalimide to form 3-phenylselenio-pyrroloindoline adducts, which are ionized with methyl triflate in the presence of prenyl tributylstannane.[2] Considerable preactivation attends this method, which requires stoichiometric use of both tin and selenium reagents, as well as protection of the indolic nitrogen.

In the course of studies aimed at the development of C−C bond-forming hydrogenations beyond hydroformylation,[3] we recently developed a suite of catalytic methods for carbonyl allylation,[4b,d−f,i−k] crotylation,[4b,c,g,k] and reverse prenylation[4a,b,h,k] in the absence of stoichiometric allylmetal reagents. In the specific case of reverse prenylation,[4a,b,h,k] it was found that reductive C−C bond formation is achieved

(1) For selected reviews encompassing the synthesis and biosynthesis of prenylated indole alkaloids, see: (a) Williams, R. M.; Stocking, E. M.; Sanz-Cervera, J. F. *Top. Curr. Chem* **2000**, *209*, 97. (b) Williams, R. M. *Chem. Pharm. Bull.* **2002**, *50*, 711. (c) von Nussbaum, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 3068. (d) Williams, R. M.; Cox, R. J. *Acc. Chem. Res.* **2003**, *36*, 127. (e) Steffan, N.; Grundmann, A.; Yin, W.-B.; Kremer, A.; Li, S.-M. *Curr. Med. Chem.* **2009**, *16*, 218.

(2) For application of this strategy toward the synthesis of 3-*tert*-prenylated indoles, see: (a) Amauramine and ardeemin families of natural products: Marsden, S. P.; Depew, K. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1994**, *116*, 11143. (b) Depew, K. M.; Marsden, S. P.; Zatorska, D.; Zatorski, A.; Bornmann, W. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11953. (c) Roquefortine family of natural products: Chen, W.-C.; Joullié, M. M. *Tetrahedron Lett.* **1998**, *39*, 8401. (d) Schiavi, B.; Richard, D. J.; Joullié, M. M. *J. Org. Chem.* **2002**, *67*, 620. (e) Richard, D. J.; Schiavi, B.; Joullié, M. M. *Proc. Nalt. Acad. Sci. U.S.A.* **2004**, *101*, 11971. (f) Shangguan, N.; Hehre, W. J.; Ohlinger, W. S.; Beavers, M. P.; Joullié, M. M. *J. Am. Chem. Soc.* **2008**, *130*, 6281. (g) The oxaline and neoxaline: Sunazuka, T.; Shirahata, T.; Tsuchiya, S.; Hirose, T.; Mori, R.; Harigaya, Y.; Kuwajima, I.; Ohmura, S. *Org. Lett.* **2005**, *7*, 941.

10.1021/ol9018562 CCC: $40.75
Published on Web 09/18/2009

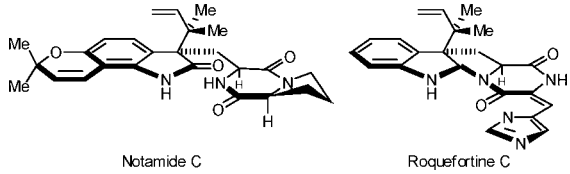
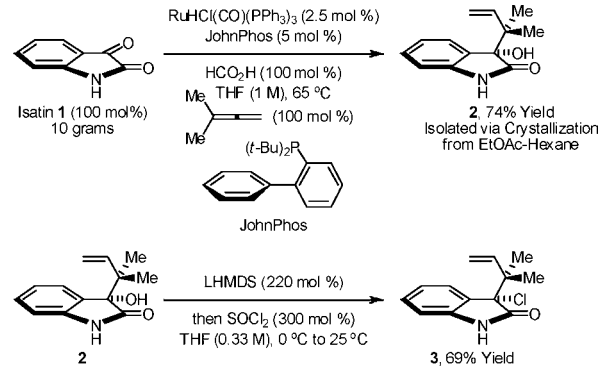


Figure 1. Examples of indole alkaloids that incorporate a *tert*-prenyl moiety at the indole 3-position.

simply upon hydrogenation[4a] or transfer hydrogenation[4b,h,k] of 1,1-dimethylallene in the presence of carbonyl partners, including isatins.[4a,k] Although the synthesis of 3-*tert*-prenylated oxindoles can be achieved through the addition of prenylindium reagents to isatins[5] or through enolate-Claisen rearrangement,[6] *N*-protected isatins are generally required.[7,8e]

Here, we report that under the conditions of ruthenium catalyzed transfer hydrogenation, direct *tert*-prenylation of isatin occurs in the absence of *N*-protecting groups. Furthermore, the resulting adduct, 3-hydroxy-3-*tert*-prenyl-oxindole **2**, is readily converted to the chloride **3**, which engages in tertiary neopentyl substitution with *C*-nucleophiles to furnish adducts possessing two contiguous all-carbon quaternary centers, presumably by way of an aza-*o*-xylylene intermediate.[8,9] To our knowledge, these studies represent the first general protocol for intermolecular substitution in a tertiary neopentyl system.[10,11]

Scheme 1. Reverse Prenylation of Isatin **1** and Conversion to 3-Chloro-3-*tert*-prenyl oxindole **3**[a]



[a] Compound **2** was isolated by crystallization from ethyl acetate−hexane. Compound **3** was isolated by silica gel chromatography. See Supporting Information for experimental details.

Our initial studies focused on the reaction of isatin **1** with 1,1-dimethylallene under the conditions of ruthenium-catalyzed transfer hydrogenation. Our prior work on allene couplings of this type took advantage of a catalyst derived from $RuBr(CO)_3(\eta^3\text{-}C_3H_5)$ and *t*-$BuPPh_2$ in combination with isopropanol as terminal reductant.[12] For the present study, a process better suited to gram scale synthesis was sought. Hence, our optimization focused on the use of commercially available $RuHCl(CO)(PPh_3)_3$ as precatalyst. For this catalyst precursor, formic acid was found to be superior to isopropanol as terminal reductant. Additionally, the choice of ligand proved to be crucial. Use of $RuHCl(CO)(PPh_3)_3$ in the absence of added ligand did not result in product formation. However, use of $RuHCl(CO)(PPh_3)_3$ in the presence of more electron-rich phosphines, such as tris(4-methoxyphenyl)phosphine or JohnPhos, provided the desired product of *tert*-prenylation **2** in isolated yields of 61% and 74%, respectively, at catalyst loadings of 2.5 mol % employing equimolar quantities of isatin **1**, 1,1-dimethylallene, and formic acid at 65 °C. The latter conditions employing JohnPhos as ligand were employed on 10 g scale with isolation of the product via crystallization from ethyl acetate−hexane (Scheme 1).

With gram quantities of alcohol **2** in hand, methods for the synthesis of tertiary neopentyl chloride **3** were explored. Standard conditions employing thionyl chloride and a tertiary amine base led to isolated yields ranging between 30% and

(3) For selected reviews on C−C bond-forming hydrogenation and transfer hydrogenation, see: (a) Ngai, M.-Y.; Kong, J. R.; Krische, M. J. *J. Org. Chem.* **2007**, *72*, 1063. (b) Skucas, E.; Ngai, M.-Y.; Komanduri, V.; Krische, M. J. *Acc. Chem. Res.* **2007**, *40*, 1394. (c) Shibahara, F.; Krische, M. J. *Chem. Lett.* **2008**, *37*, 1102. (d) Bower, J. F.; Kim, I. S.; Patman, R. L.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 34.

(4) (a) Skucas, E.; Bower, J. F.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 12678. (b) Bower, J. F.; Skucas, E.; Patman, R. L.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 15134. (c) Shibahara, F.; Bower, J. F.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 6338. (d) Kim, I. S.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 6340. (e) Kim, I. S.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 14891. (f) Lu, Y.; Kim, I.-S.; Hassan, A.; Del Valle, D. J.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 5018. (g) Kim, I. S.; Han, S.-B.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 2514. (h) Han, S.-B.; Kim, I. S.; Han, H.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 6916. (i) Lu, Y.; Krische, M. J. *Org. Lett.* **2009**, *11*, 3108. (j) Hassan, A.; Lu, Y.; Krische, M. J. *Org. Lett.* **2009**, *11*, 3112. (k) Itoh, J.; Han, S. B.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 6316.

(5) Nair, V.; Ros, S.; Jayan, C. N.; Viji, S. *Synthesis* **2003**, 2542.

(6) (a) Malapel-Andrieu, B.; Piroëlle, S.; Mérour, J.-Y. *J. Chem. Res.* **1998**, 594. (b) Kawasaki, T.; Nagaoka, M.; Satoh, T.; Okamoto, A.; Ukon, R.; Ogawa, A. *Tetrahedron* **2004**, *60*, 3493.

(7) As described in ref 8e, treatment of 3-methyl-3-bromo-oxindole with *n*-prenyl tributylstannane delivers the 3-methyl-3-*tert*-prenyl-oxindole in the absence of an *N*-protecting group. However, stoichiometric quantities of tin byproducts are generated.

(8) While many substitution reactions involving *C*-nucleophiles and 3-substituted-3-halo-oxindoles are reported, examples of tertiary neopentyl substitution are absent. While in earlier literature aza-xylylene intermediates are not proposed as intermediates (e.g. refs a−c), their intervention is possible and highly likely: (a) Labroo, R. B.; Labroo, V. M.; King, M. M.; Cohen, L. A. *J. Org. Chem.* **1991**, *56*, 3637. (b) Kobayashi, M.; Aoki, S.; Gato, K.; Matsunami, K.; Kurosu, M.; Kitagawa, I. *Chem. Pharm. Bull.* **1994**, *42*, 2449. (c) Rajeswaran, W. G.; Labroo, R. B.; Cohen, L. A. *J. Org. Chem.* **1999**, *64*, 1369. (d) Fuchs, J. R.; Funk, R. L. *J. Am. Chem. Soc.* **2004**, *126*, 5068. (e) Fuchs, J. R.; Funk, R. L. *Org. Lett.* **2005**, *7*, 677. (f) England, D. B.; Merey, G.; Padwa, A. *Org. Lett.* **2007**, *9*, 3805. (g) England, D. B.; Merey, G.; Padwa, A. *Heterocycles* **2007**, *74*, 491. (h) Krishnan, S.; Stoltz, B. M. *Tetrahedron. Lett.* **2007**, *48*, 7571.

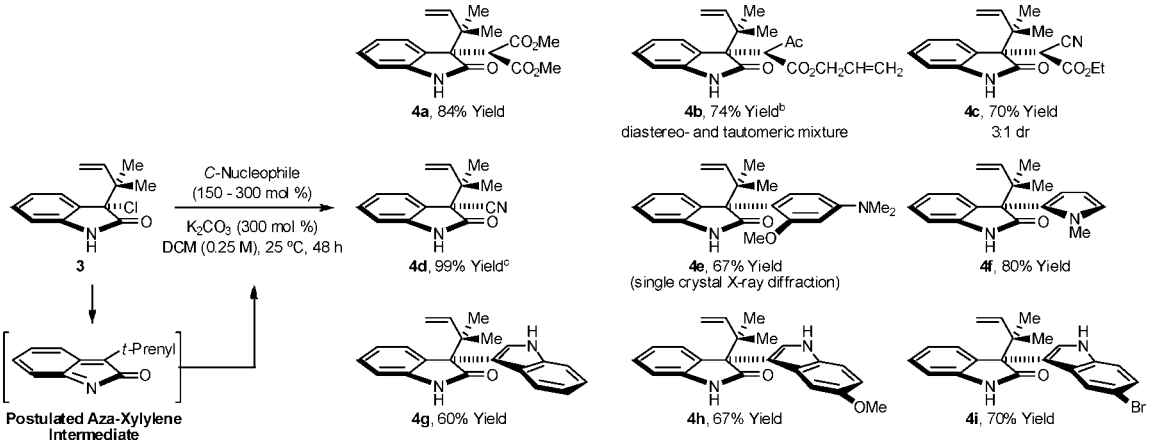
(9) For a seminal observation of substitution reactions involving heteroatom nucleophiles and 3-halo-oxindoles, see: Hinman, R. L.; Bauman, C. P. *J. Org. Chem.* **1964**, *29*, 2431. Intervention of aza-xylylene intermediates is not proposed yet is highly probable.

(10) For selected examples of primary neopentyl substitution reactions, see: (a) Lewis, R. G.; Gustafson, D. H.; Erman, W. F. *Tetrahedron Lett.* **1967**, *8*, 401. (b) Paquette, L. A.; Philips, J. C. *Tetrahedron Lett.* **1967**, *8*, 4645. (c) Weiss, R. G.; Snyder, E. I. *J. Org. Chem.* **1971**, *36*, 403. (d) Stephenson, B.; Solladie, G.; Mosher, H. S. *J. Am. Chem. Soc.* **1972**, *94*, 4184. (e) Anderson, P. H.; Stephenson, B.; Mosher, H. S. *J. Am. Chem. Soc.* **1974**, *96*, 3171.

(11) For reviews encompassing neopentyl substitution, see: (a) Mosher, H. S. *Tetrahedron* **1974**, *30*, 1733. (b) Rossi, R. A.; Postigo, A. I. *Curr. Org. Chem.* **2003**, *7*, 747.

(12) For ruthenium catalyzed reductive coupling of 1,1-disubstituted allenes to paraformaldehyde and higher aldehydes, see: Ngai, M.-Y.; Skucas, E.; Krische, M. J. *Org. Lett.* **2008**, *10*, 2705.

Scheme 2. Tertiary Neopentyl Substitution of Chloride **3** to Furnish Adducts **4a**−**4i** Possessing Contiguous All-Carbon Quaternary Centers[a]



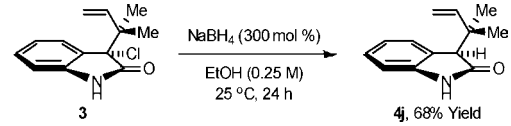
[a] For adducts **4a**−**4f**, 300 mol % NuH was employed. For adducts **4g**−**4i**, 150 mol % NuH was employed. Cited yields are of material isolated by silica gel chromatography. See Supporting Information for experimental details. [b] Obtained as a mixture of diastereomers and keto-enol tautomers. [c] For the formation of **4d**, 10 mol % Bu_4NI, THF−H_2O (1:3) was used as solvent and the reaction was run for 24 h.

90%. However, the desired chloride **3** was contaminated with substantial quantities of Wagner−Meerwein product. It was postulated that Wagner−Meerwein rearrangement occurs upon ionization of the transient chlorosulfite to form the protonated aza-*o*-xylylene. Based on this interpretation, irreversible dianion formation followed by the addition of thionyl chloride should generate a transient chlorosulfite that should eliminate to furnish a neutral aza-*o*-xylylene, which should be less susceptible to Wagner−Meerwein shift. Indeed, treatment of alcohol **2** with 2.2 equiv of LHMDS followed by thionyl chloride provided the tertiary neopentyl chloride **3** in 69% yield as a single constitutional isomer (Scheme 1).

Acquisition of chloride **3** set the stage for tertiary neopentyl substitution. Upon exposure of chloride **3** to dimethyl malonate in the presence of potassium carbonate in dichloromethane solvent,[8] the desired product of tertiary neopentyl substitution **4a** was obtained in 84% isolated yield. These conditions were applied to a range of *C*-nucleophiles. As demonstrated by the formation of adducts **4a**−**4i**, active methylene compounds, cyanide, and electron-rich arenes engage in efficient tertiary neopentyl substitution with chloride **3** (Scheme 2). Finally, sodium borohydride reduction of chloride **3** also is possible, as demonstrated by the formation of **4j** (Scheme 3).

In summary, we report a protecting-group-free method for the gram-scale synthesis of 3-hydroxy-3-*tert*-prenyl-oxindole **2** via ruthenium-catalyzed C−C bond-forming transfer hydrogenation. Conditions were identified for the conversion

Scheme 3. Dehalogenation of Chloride **3** Mediated by $NaBH_4$[a]



[a] As described in Scheme 2.

of tertiary neopentyl alcohol **2** to the corresponding chloride **3** in the absence of Wagner−Meerwein shift. Finally, chloride **3** engages in tertiary neopentyl substitution by way of an aza-*o*-xylylene intermediate to furnish the *tert*-prenylated oxindoles **4a**−**4i**. Future studies will focus on the development of related asymmetric neopentyl substitutions and application of these methods toward the synthesis of naturally occurring 3-*tert*-prenylated indoles.

Acknowledgment. The Robert A. Welch Foundation and the NIH-NIGMS (R01-GM069445-S109) are acknowledged for partial support of this research.

Supporting Information Available: Spectral data for all new compounds (^1H NMR, ^{13}C NMR, IR, HRMS). Single crystal X-ray diffraction data for **4e**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9018562