JOC*Note*

Direct N-Carbamoylation of 3-Monosubstituted Oxindoles with Alkyl Imidazole Carboxylates

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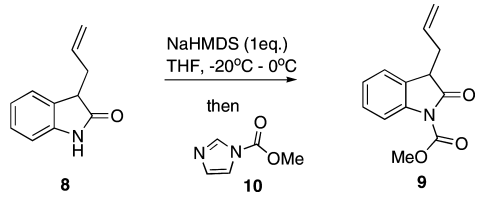
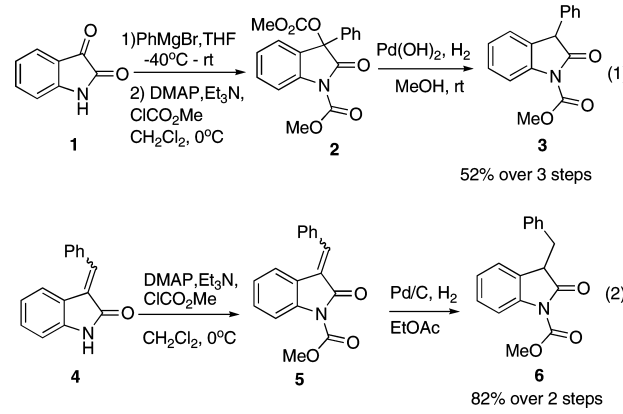
Received April 16, 2009



Regioselective N-carbamoylation of oxindoles was achieved through the use of imidazole carboxylate reagents. This reaction provides ready access to N-carbamoyl-3-monosubstituted oxindoles.

Prochiral 3-monosubstituted oxindoles are important precursors for the preparation of oxindole and indoline natural products.[1] Catalytic asymmetric functionalization of 3-monosubstituted oxindoles via allylic alkylation,[2] acyl transfer,[3] fluorination,[4] hydroxylation,[5] aldol reaction,[6] or Claisen rearrangement[7] has allowed the preparation of chiral oxindoles bearing stereogenic tertiary or quaternary centers at the 3 position. It has been reported that the reactivity and selectivity of many of these reactions is dependent on the substitution at nitrogen of the oxindole.[1c,4a,5a,6b] In several cases, N-carbamoyl, such as N-Boc, protected oxindoles showed superior selectivity than those with N-alkyl substitutions (N-methyl or N-benzyl). The methoxycarbonyl (Moc) group, which is electronically similar to the Boc group but sterically smaller, has been frequently employed as a protecting group for nitrogen.[8] Surprisingly, very few N-Moc protected oxindoles are known in the literature and to the best of our knowledge, they have not been examined as substrates in any catalytic asymmetric reactions.[9] Development of a convenient and general method for the synthesis of N-Moc protected oxindoles should allow for the examination of these entities as nucleophiles in asymmetric synthesis.

SCHEME 1. Synthesis of N-Moc Oxindoles



We initially examined the preparation of the N-Moc oxindoles based on the literature reports for the preparation of N-Boc oxindoles. Direct Boc protection of N−H-3-monosubstituted oxindoles was reported to be problematic due to competitive O- and C-reactivity.[10] To circumvent the problem, Sodeoka has developed a three-step sequence involving Grignard addition to isatin followed by Boc protection and deoxygenation under hydrogenolysis conditions.[4a] Alternatively, it has also been reported that Boc protection of a 3-benzylidene oxindole followed by hydrogenation of the double bond afforded an N-Boc-3-benzyl-oxindole.[5a] We found that both of these methods can be modified for the synthesis of N-Moc protected oxindoles by substituting Boc anhydride with chloro methylformate (eqs 1 and 2, Scheme 1). However, both methods have significant limitations. The approach starting from isatin is limited by the availability of the Grignard reagent, and the second method requires an alkylidene-substituted oxindole as precursor.[4] Moreover, both methods employ a hydrogenation reaction to form the final product and thus functional groups such as alkene, alkynes, and aromatic halides are not tolerated. For maximum flexibility, a direct carbamoylation of an N−H oxindole such as **8** would be most desirable.

The N−H oxindoles are easily prepared by either oxidation of the corresponding indoles,[12] monoalkylation of the dianions of the unsubstituted oxindole,[13] or cross-coupling chemistry.[14] For example, treatment of commercially available oxindole **7**

(1) (a) Lebsack, A. D.; Link, J. T.; Overman, L. E.; Stean, B. A. *J. Am. Chem. Soc.* **2002**, *124*, 9008. (b) Lakshmaiah, G.; Kawabata, T.; Shang, M.; Fuji, K. *J. Org. Chem.* **1999**, *64*, 1699. (c) Trost, B. M.; Brennan, M. K. *Org. Lett.* **2006**, *8*, 2027. (d) Overman, L. E.; Shin, Y. *Org. Lett.* **2007**, *9*, 339. (e) Trost, B. M.; Stiles, D. T. *Org. Lett.* **2007**, *9*, 2763.

(2) (a) Trost, B. M.; Frederiksen, M. U. *Angew. Chem., Int. Ed.* **2005**, *44*, 308. (b) Trost, B. M.; Zhang, Y. *J. Am. Chem. Soc.* **2006**, *128*, 4590. (c) Trost, B. M.; Zhang, Y. *J. Am. Chem. Soc.* **2007**, *129*, 14548.

(3) (a) Shaw, S. A.; Aleman, P.; Vedeis, E. *J. Am. Chem. Soc.* **2003**, *125*, 13368. (b) Hills, I. D.; Fu, G. C. *Angew. Chem. Int. Ed.* **2003**, *42*, 3921.

(4) (a) Hamashima, Y.; Suzuki, T.; Takano, H.; Shimura, Y.; Sedeoka, M. *J. Am. Chem. Soc.* **2005**, *127*, 10164. (b) Ishimaru, T.; Shibata, N.; Horikawa, T.; Yasuda, N.; Nakamura, S.; Toru, T.; Shiro, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4157.

(5) (a) Ishimaru, T.; Shibata, N.; Nagai, J.; Nakamura, S.; Toru, T.; Kanemasa, S. *J. Am. Chem. Soc.* **2006**, *128*, 16488. (b) Sano, D.; Nagata, K.; Itoh, T. *Org. Lett.* **2008**, *10*, 1593.

(6) (a) Ogawa, S.; Shibata, N.; Inagaki, J.; Nakamura, S.; Toru, T.; Shiro, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 8666. (b) Tian, X.; Jiang, K.; Peng, J.; Du, W.; Chen, Y.-C. *Org. Lett.* **2008**, *10*, 3583.

(7) Linton, E. C.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 16162.

(8) Corey, E. J.; Bock, M. G.; Kozikowski, A. P.; Rao, A. V. R.; Floyd, D.; Lipshutz, B. *Tetrahedron Lett.* **1978**, 1051.

(9) Our group has recently reported the use of N-Moc-3-alkylideneoxindoles as substrates for asymmetric TMM reactions: Trost, B. M.; Cramer, N.; Silverman, S. M. *J. Am. Chem. Soc.* **2007**, *129*, 12396.

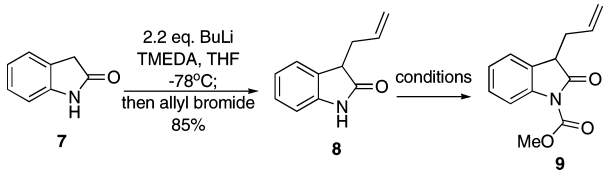
(10) Rajeswaran, W. G.; Cohen, L. A. *Tetrahedron* **1998**, *54*, 11375.

(11) Huang, A.; Kodanko, J. J.; Overman, L. E. *J. Am. Chem. Soc.* **2004**, *126*, 14043.

(12) Szabó-Pusztay, Z.; Szabó, L. *Synthesis* **1979**, 276.

10.1021/jo900760r CCC: $40.75
Published on Web 06/02/2009

TABLE 1. Optimizations Studies



entry	conditions	yield of **9**
1	$ClCO_2Me$ (1 equiv), NEt_3, DMAP (0.1 equiv), CH_2Cl_2, 0 °C	~15%
2	NaHMDS (1 equiv), $ClCO_2Me$, THF, 0 °C	~25%
3	NaHMDS (1 equiv), **10**, THF, 0 °C	86%

with excess BuLi in the presence of TMEDA generates the dianion of **7**. Quenching the dianion with allyl bromide afforded the monoallylated oxindole **8** in good yield (Table 1). Disappointingly, the reaction of oxindole **8** with methyl chloroformate under a variety of conditions failed to provide the desired N-Moc product cleanly (entries 1 and 2, Table 1). Similar to previous reports of Boc protection of 3-monosubstituted-N−H oxindoles, products of O-acylation and bis-acylation accounted for most of the mass balance. We reasoned that a "softer" acylating reagent should help differentiate N from O. Several literature reports indicate that an imidazole analog of methyl chloroformate is a "softer" electrophile and thus should favor selective N-acylation.[15,16] Indeed, subjecting the Na salt of oxindole **8** to 1 equiv of imidazole carboxylate **10** at 0 °C in THF afforded the mono-N-carbamoylated product selectively in 86% yield.

The use of imidazole carboxylate **10** to prepare N-Moc oxindoles with varying substitution patterns was then investigated (Table 2). Both alkyl and aryl substitution at the 3 position were tolerated (entry **11h**). Oxindoles with ring-substitutions also performed well (entries **11d** and **11f**). It should be noted that more stabilized oxindole anions required higher temperature to react (entries **11d** and **11h**).

Alkoxycarbonyl groups other than methoxycarbonyl can also be installed selectively using the imidazole carboxylate reagents as the electrophile (Table 3). The required imidazole carboxylates were prepared by simply mixing the corresponding chloroformate with 2 equiv of imidazole in THF followed by filtration and removal of the solvent (Scheme 2).[16] Treatment of the resulting imidazole carboxylates with the Na salt of oxindole **8** furnished N-carbamoyl oxindoles selectively in good to excellent yields.

In summary, we have developed a convenient and general procedure for the synthesis of N-carbamoyl-3-monosubstituted oxindoles.[17] Both the N−H oxindole precursor and the imidazole carboxylate reagents are readily available.[16] The carbamoylation reaction is highly selective at the N with the imidazole reagent compared to the reaction with the more commonly employed chloroformate reagent, where a mixture of products are obtained.

TABLE 2. Synthesis of N-Moc Protected Oxindoles

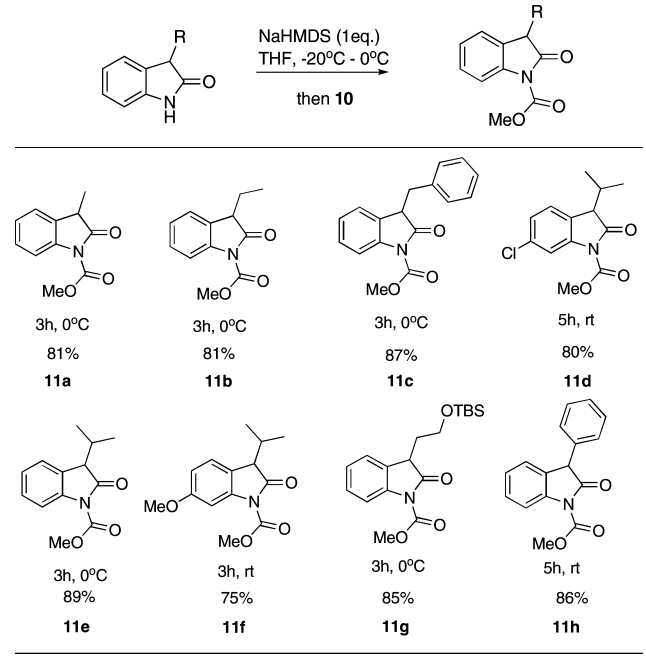
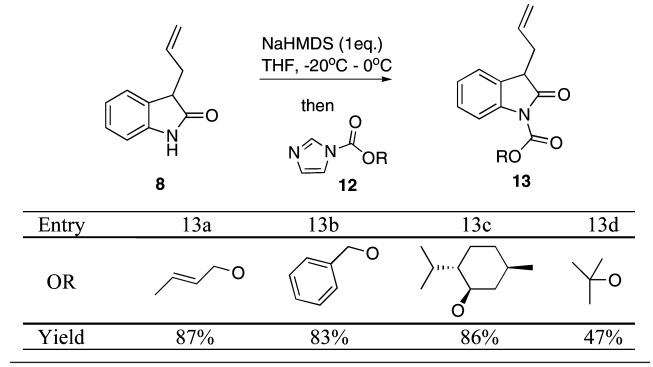
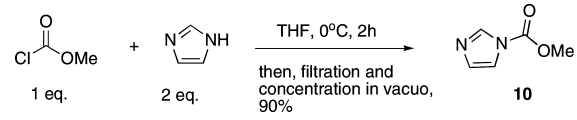


TABLE 3. Synthesis of N-Carbamate Protected Oxindoles



SCHEME 2. Synthesis of Imidazole Carboxylate 10



This method does not require the use of a hydrogenation reaction, and hence is broadly applicable to substrates with sensitive functional groups. The studies of N-Moc-3-monosubstituted oxindoles as nucleophiles in allylic alkylation reactions are ongoing.[18]

Experimental Section

Synthesis of imidazole carboxylate **10**: To a solution of imidazole (8.55 g, 100 mmol) in THF (120 mL) was added methyl chloroformate (5.2 g, 55 mmol) at 0 °C. The resulting solution was stirred at 0 °C for 3 h before it was filtered under a stream of N_2. The filtrate was concentrated *in vacuo* to afford **10** (5.19 g, 82% yield) as a white solid. IR (film) λ_{max}/cm^{-1}: 3130, 1763, 1475, 1443, 1384, 1291, 1246, 1009. ^1H NMR (500 MHz, $CDCl_3$): δ 8.15 (s, b, 1H), 7.44 (s, b, 1H), 7.07 (s, b, 1H), 4.04(s, 3H);^{13}C NMR (125 MHz,

(13) Kende, A. S.; Hodges, J. C. *Synth. Commun.* **1982**, *12*, 1.
(14) Altman, R. A.; Hyde, A. M.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 9613.
(15) (a) Staab, H. A. *Angew. Chem., Int. Ed. Engl.* **1962**, *7*, 350. (b) Shone, R. L.; Deason, J. R.; Miyano, M. *J. Org. Chem.* **1986**, *51*, 268. (c) Werner, T.; Barrett, A. G. M. *J. Org. Chem.* **2006**, *71*, 4302. (d) Toullec, P. Y.; Bonaccorsi, C.; Mezzetti, A.; Togni, A.; Trost, B. M. *Proc. Natl. Acad. Sci.* **2004**, *101*, 5810. (e) Trost, B. M.; Xu, J. *J. Org. Chem.* **2007**, *72*, 9372.
(16) Nimitz, J. S.; Mosher, H. S. *J. Org. Chem.* **1981**, *46*, 211. Alternatively, imadazole carboxylates can be prepared by reaction of the corresponding alcohol and 1,1′-carbonyldiimidazole: see ref 14.
(17) In the Supporting Information of ref 4a, Sodeoka reported two examples of the acylation of 3-(*o*-anisyl)oxindole in 42 and 70% yield. We thank one of the referees for alerting us to these two cases.
(18) For a standard deprotection procedure of N-Moc-oxindole, see Supporting Information.

$CDCl_3$) δ 149.0, 136.9, 130.4, 116.9, 54.5. This material underwent slow decarboxylation at rt and was stored at −20 °C.

Synthesis of N-Moc-3-allyl oxindole **9**. To a solution of oxindole (400 mg, 3 mmol) in THF (20 mL) was added TMEDA (1.5 mL, 10 mmol), and the resulting solution was cooled to −78 °C. BuLi (2.6 mL, 2.5 M in hexane) was added dropwise and the resulting solution was stirred for 30 min allyl bromide (600 mg, 5 mmol) was then added dropwise and the solution was slowly warmed up to −20 °C and stirred for 3 h at that temperature. The reaction was then quenched with aq. NH_4Cl (20 mL) and extracted with ethyl acetate (3 × 25 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in *vacuo*. Purification through silica gel (30% EtOAc-pentane) afforded 3-allyloxindole (340 mg, 67%). On a 30 mmol scale, an 85% yield was obtained as detailed in the Supporting Information.

3-Allylloxindole (340 mg, 2.0 mmol) was dissolved in 15 mL dry THF and cooled to −20 °C. A freshly prepared solution of NaHMDS (420 mg, 2.2 mmol, 95%) in THF (5 mL) was added dropwise. The resulting solution was stirred for 30 min and a solution of **10** (280 mg, 2.2 mmol) in THF (3 mL) was added dropwise. The resulting solution was slowly warmed up to 0 °C and stirred for 3 h. The reaction was quenched with dropwise addition of AcOH (0.5 mL) in THF (2 mL) and then 20 mL water. The mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in *vacuo*. Purification through silica gel (20% EtOAc−pentane) afforded **9** as a clear oil (400 mg, 86%). IR (film) λ_{max}/cm^{-1}: 2964, 2878, 1771, 1735, 1607, 1467, 1439, 1354, 1297, 1242, 1155, 1094, 1052, 1024, 911, 761; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91(d, J = 8.5, 1H), 7.36−7.28(m, 2H), 7.18(t, J = 7.5, 1H), 5.75−5.67 (m, 1H), 5.12(dm, J = 17, 1H), 5.07(dm, J = 10, 1H), 4.02 (s, 3H), 3.67(t, J = 5.5, 1H), 2.87−2.81 (m, 1H), 2.70−2.63(m, *1H*),;^{13}C NMR (125 MHz, $CDCl_3$) δ 175.4, 151.6, 139.7, 133.1, 128.4, 127.4, 124.7, 119.0, 115.1, 54.0, 45.8, 35.6. HRMS (MNa^+): calcd for $C_{13}H_{13}NO_3$: 231.0895; found: 231.0892.

Acknowledgment. We thank the National Science Foundation and the National Institute of Health, Gneral Medical Sciences Grant GM 13598, for their generous support of our programs. Dr. Jiayi Xu is acknowledged for giving us imidazole carboxylate reagent **12a**. Dr. Benjamin Taft is acknowledged for proofreading the manuscript.

Supporting Information Available: Full experimental details, spectral data, and characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO900760R