ORGANIC LETTERS

2010
Vol. 12, No. 2
392−395

Indium Triflate-Assisted Nucleophilic Aromatic Substitution Reactions of Nitrosobezene-Derived Cycloadducts with Alcohols

Baiyuan Yang and Marvin J. Miller*

Department of Chemistry and Biochemistry, 251 Nieuwland Science Hall, University of Notre Dame, Notre Dame, Indiana 46556

mmiller1@nd.edu

Received December 1, 2009

ABSTRACT

Exclusive nucleophilic aromatic substitution of hydrogen in conjunction with cleavage of the N−O bond was observed when nitrosobenzene-derived nitroso cycloadducts were treated with indium triflate in the presence of alcohols. Aromatic alkoxylated *syn*-1,4 aminocycloalkenol products with good to excellent regioselectivity (16:84 to 0:100, ortho:para) were obtained.

Nitroso cycloadducts **1** (Scheme 1), derived from nitroso Diels−Alder reactions (NDA),[1] are valuable synthetic intermediates as they serve as a general scaffold to create unique structural and functional diversity. Several modes of ring-opening reactions of bicyclic oxazines **1** have been established to introduce different functionalities with defined stereo- and regiochemistries.[2] For example, the C−O bond cleavage of **1a** and**1b** may be induced by Lewis acids to selectively give hydroxamate or hydroxyamino containing *anti*-1,2-, *anti*-1,4-, and *syn*-1,4-alkoxylated cycloalkenes (Scheme 1, routes A and B).[2d,e] The reactivity and stereoselectivity have been demonstrated to depend on the binding ability of Lewis acids with oxazines. Nitrosobenzene-derived cycloadducts (**1c**,**d**) are unique substrates for this chemistry, since in contrast to **1a** and **1b**, they do not contain additional coordination center(s) attached to the oxazine core. In fact, this apparently simple difference has significant chemical consequences. Here we report the first example of indium triflate-assisted nucleophilic aromatic substitution (S_NAr) of **1c**,**d** in the presence of alcohols. Nucleophilic aromatic substitution reaction[3] occurs at electron-deficient aromatic rings and typically involves displacement of halogens or other nucleofugal groups. The reactions described here are unusual in that they involve an S_NAr reaction with net replacement of hydrogen[4] via a concomitant N−O bond cleavage to afford aromatic alkoxylated *syn*-1,4 aminocycloalkenol products **4** and/or **5** in one step (Scheme 1, route C).

Our studies began with an initial experiment with nitroso cycloadduct **1c** derived from NDA reaction of nitrosobenzene with cyclopentadiene. While the cycloadduct could be

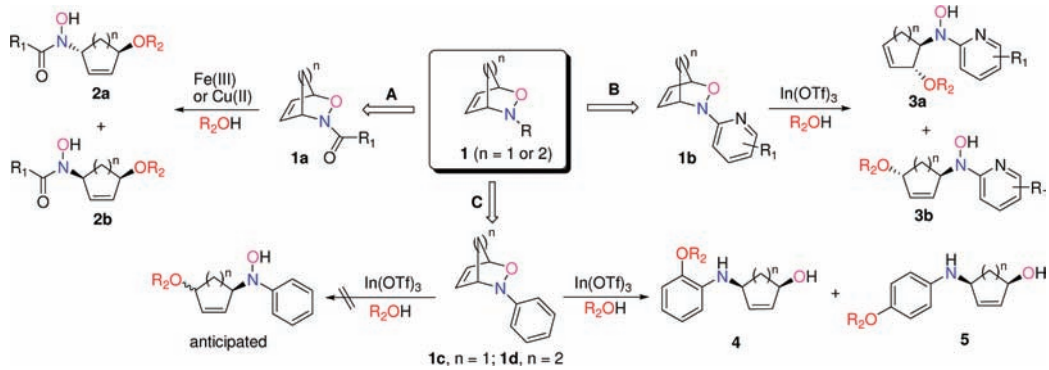
(1) (a) Vogt, P. F.; Miller, M. J. *Tetrahedron* **1998**, *54*, 1317–1348. (b) Yamamoto, Y.; Yamamoto, H. *Eur. J. Org. Chem.* **2006**, 2031–2043. (c) Samarakoon, T.; Hanson, R. R. *Chemtracts* **2007**, *20*, 220–229. (d) Iwasa, S.; Fakhruddin, A.; Nishiyama, H. *Mini-Rev. Org. Chem.* **2005**, *2*, 157–175.

(2) For ring-opening with Pd(0), ruthenium, and rhodium see: (a) Tardibono, L. P.; Miller, M. J. *Org. Lett.* **2009**, *11*, 1575–1578. (b) Machin, B. P.; Howell, J. H.; Mandel, J.; Bianchard, N.; Tam, W. *Org. Lett.* **2009**, *11*, 2077–2080. (c) Machin, B. P.; Ballantine, M.; Mandel, J.; Bianchard, N.; Tam, W. *J. Org. Chem.* **2009**, *74*, 7261–7266. For ring-opening with Lewis acids, see: (d) Surman, M. D.; Miller, M. J. *J. Org. Chem.* **2001**, *66*, 2466–2469. (e) Yang, B. Y.; Miller, M. J. *J. Org. Chem.* **2009**, *74*, 7990–7993. For ring-opening with palladium/indium, see: (f) Cesario, C.; Miller, M. J. *Org. Lett.* **2009**, *11*, 1293–1295. (g) Lee, W.; Kim, K.-H.; Surman, M. D.; Miller, M. J. *J. Org. Chem.* **2003**, *68*, 139–149.

(3) (a) Miller, J. *Aromatic Nucleophilic Substitution*; Eaborn, C., Chapman, N. B., Eds.; Elsevier: New York, 1968. (b) Terrier, F. *Nucleophilic Aromatic Substitutions: The Influence of Nitro Group*; VCH: New York, 1991.

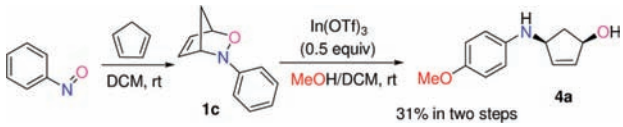
10.1021/ol9027607
Published on Web 12/15/2009

Scheme 1. Lewis Acid-Mediated Ring-Opening Reactions of Nitroso Cycloadduct **1**



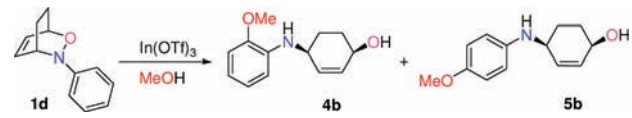
formed, the thermal instability of **1c** required that it be treated directly, without isolation, with $In(OTf)_3$ and MeOH. The reaction produced a complex mixture; however, to our surprise, a *p*-methoxylated benzene-substituted *syn*-1,4 aminocyclopentenol product, **4a**, as a net result of nucleophilic aromatic substitution and N−O bond cleavage, was isolated in 31% yield after 12 h (Scheme 2).

Scheme 2. $In(OTf)_3$-Assisted Nucleophilic Aromatic Substitution of **1c** in the Presence of MeOH



This finding encouraged us to examine the reaction with more stable, isolable [2.2.2] bicyclic nitroso adduct **1d** (Table 1). Reaction of **1d** in MeOH with 0.5 equiv of $In(OTf)_3$ at room temperature occurred, generating a 24% yield of a 15:85 ratio of *o*- and *p*-methoxylated products, **4b** and **5b**, after prolonged reaction (48 h, entry 1). Again, in contrast to reactions with acyl- and iminonitroso adducts (**1a** and **1b**), no C−O bond cleaved product was detected by LC/MS and ^{1}H NMR. Compounds **4b** and **5b** were readily separable by column chromatography, and their structures were further confirmed by 1D and 2D NMR experiments (COSY, HSQC). Variation of the amount of $In(OTf)_3$ used in the reaction at different temperature was then explored (entries 2−7). Optimized reaction conditions were found when 0.5 equiv of $In(OTf)_3$ was added to **1d**

Table 1. Optimization of $In(OTf)_3$-Assisted Nucleophilic Aromatic Substitution of **1d** in the Presence of MeOH



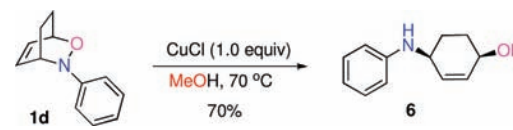
entry	$In(OTf)_3$ loading[a] (equiv)	temp (°C)	time (h)	yield[b] (%)	ratio of[c] **4b**:**5b**
1	0.5	25	48	24	15:85
2	1.0	25	24	69	18:82
3	1.5	25	12	65	18:82
4	0.5	40	24	62	12:87
5	0.2	70	24	57	16:84
6	0.5	70	2	71	16:84
7	1.0	70	2	58	17:83

[a] Relative to cycloadduct **1d**. [b] Isolated yields. [c] Determined by ^{1}H NMR of crude mixture.

at 70 °C. This gave **4b** and **5b** in a 16:84 ratio and 71% isolated yield within 2 h (entry 6).

Other Lewis acids [InI_3, $La(OTf)_3$, and $FeCl_3$] were also briefly surveyed to determine the generality of nucleophilic aromatic substitution of **1d**. However, none were as effective as $In(OTf)_3$. Treatment of a methanolic solution of cycloadduct **1d** with InI_3 or $La(OTf)_3$ at 70 °C only afforded a mixture of **4b** and **5b** in 35% and 28% yields, respectively, even after 24 h. Use of $FeCl_3$ gave only a trace amount of product. When CuCl was employed, instead of nucleophilic aromatic substitution, a simple N−O bond cleavage occurred, generating *syn*-1,4 aminocyclopentenol **6** in 70% yield (Scheme 3). These experiments indicated that the S_NAr

Scheme 3. Cu-Mediated N−O Bond Reductive Cleavage of **1d**

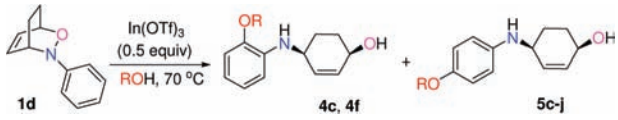


(4) For selected reviews, see: (a) Makosza, M.; Winiarski, J. *Acc. Chem. Res.* **1987**, *20*, 282–289. (b) Chupakhin, O. N.; Charushin, V. N.; Van der Plas, H. C. *Nucleophilic Aromatic Substitution of Hydrogen*; Academic Press: New York, 1994. (c) Charushin, V. N.; Chupakhin, O. N. *Mendeleev Commun.* **2007**, *17*, 249–254. For relevant publications, see: (d) Stern, M. K.; Hileman, F. D.; Bashkin, J. K. *J. Am. Chem. Soc.* **1992**, *114*, 9237–9238. (e) Soper, J. D.; Kaminsky, W.; Mayer, J. M. *J. Am. Chem. Soc.* **2001**, *123*, 5594–5595. (f) Hagel, M.; Liu, J. H.; Muth, O.; Rivera, H. J. E.; Schwake, E.; Sripanom, L.; Henkel, G.; Dyker, G. *Eur. J. Org. Chem.* **2007**, 3573–3582.

reaction here may depend on the coordinating ability of the Lewis acid, with indium triflate being optimal.

Under the optimized reaction conditions, we expanded the studies to include reactions of **1d** with several representative alcohols. The results are summarized in Table 2. Reactions of **1d** with ^{i}PrOH, 1-hexanol, and

Table 2. In(OTf)$_3$-Assisted Nucleophilic Aromatic Substitution of **1d** with Different Alcohols



entry	ROH	product	yield[b] (%)	ratio of[c] **4**:**5**
1	$(CH_3)_2CHOH$	**4c** + **5c**	58	13:87
2	$C_6H_{13}OH$	**5d**	56	0:100
3	$(CH_3)_3COH$	**5e**	37	0:100
4	$CH_2{=}CHCH_2OH$	**4f** + **5f**	68	13:87
5	$CH{\equiv}CCH_2OH$	**5g**	58	~0:100
6[a]	$C_6H_5CH_2OH$	**5h**	55	0:100
7[a]	4-$CH_3OC_6H_5CH_2OH$	**5i**	49	0:100
8[a]	4-$O_2NC_6H_5CH_2OH$	**5j**	39	0:100

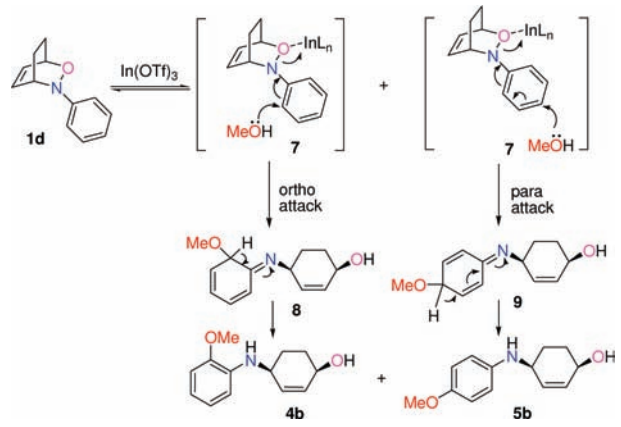
[a] 5.0 equiv of ROH in THF used. [b] Isolated yields. [c] Determined by ^{1}H NMR of crude mixutre.

^{t}BuOH afforded the corresponding aromatic alkoxylated products in moderate yields (entries 1−3). To give compounds more compatible for eventual further elaboration, reactions of **1d** with allyl alcohol, propargyl alcohol, and benzyl alcohols were performed. Reaction with allyl alcohol gave a 68% yield of a 13:87 ratio of *o*- and *p*-allyloxylated compounds **4f** and **5f** (entry 4). Only para-substituted 1,4 aminocyclohexenol **5g** was isolated in 58% yield when propargyl alcohol was used (entry 5). Reactions of **1d** with 5.0 equiv of benzyl alcohol, 4-methoxybenzyl alcohol, and 4-nitrobenzyl alcohol in THF generated exclusive *p*-benzyloxylated products **5h**, **5i**, and **5j** in 55%, 49%, and 39% yields, respectively (entries 6−8). The regioselectivity for *p*-alkoxylated product **5** over *o*-alkoxylated product **4** might result from the steric repulsion generated from the attack of alcohol at the ortho position. Treatment of **1d** with In(OTf)$_3$ in aqueous THF generated a mixture of aromatic hydroxylated *syn*-1,4 amino cycloalkenol products based on LC/MS analysis.

A control reaction was also run in which **1d** was treated with methanol in the absence of In(OTf)$_3$ at 70 °C for 12 h. Oxazine **1d** was recovered unchanged, thus indicating that chelation with indium triflate is indeed important for the reaction. A plausible mechanism for the formation of **4b** and**5b** through net nucleophilic aromatic substitution of hydrogen is proposed (Scheme 4).[5] The reaction might be initiated by coordination between the oxygen atom in

(5) Nucleophilic aromatic substitution on ester derivatives of carcinogenic *N*-arylhydroxamic acids has been reported, see: (a) Novak, M.; Rangappa, K. *J. Org. Chem.* **1992**, *57*, 1285–1290. (b) Novak, M.; Rangappa, K.; Manitssa, R. K. *J. Org. Chem.* **1993**, *58*, 7813–7821.

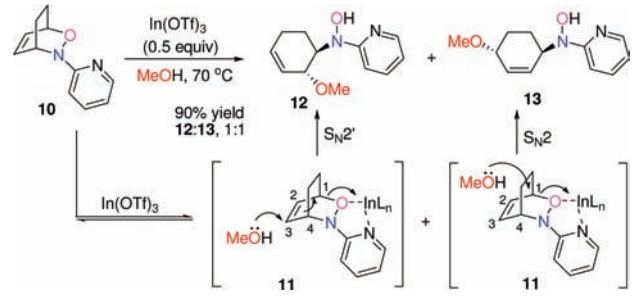
Scheme 4. Proposed Mechanism for Formation of **4b** and **5b** through In(OTf)$_3$-Assisted S$_N$Ar Reaction of **1d**



oxazine **1d** and indium to generate electron-deficient intermediate **7**, which is susceptible to the addition of methanol to the aromatic ring at either the ortho or para positions. Tautomerization of the resulting imines **8** and **9** would generate products **4b** and **5b** with concomitant rearomatization. Alternately, a S$_N$1-like mechanism involving initial N−O bond cleavage to generate a nitrene cannot be ruled out.

For comparison, iminonitroso cycloadduct **10** was synthesized and subjected to the same reaction conditions (Scheme 5). Consistent with our previous report,[2e] only

Scheme 5. Proposed Mechanism for Formation of **12** and **13** through In(OTf)$_3$-Mediated C−O Bond Cleavage of **10**



C−O bond cleaved products, *anti*-1,2-**12** and *anti*-1,4-**13**, were obtained in 90% yield and in a 1:1 ratio. The likely mechanism involves a formation of coordinated intermediate **11** as a result of a five-membered ring chelation with the In, as well as a subsequent direct (S$_N$2-like) or indirect (S$_N$2′-like) nucleophilic displacement of the oxygen during the attack of methanol. These results clearly indicated that the additional chelation between indium and the imino nitrogen of oxazine finely tuned the electronic property of **10** to the favor of C−O bond cleavage.

In summary, we have demonstrated an unprecedented nucleophilic aromatic substitution reaction of nitrosobenzene-

derived cyloadducts with alcohols catalyzed by indium triflate. In most cases, regioselective para-aromatic alkoxylated *syn*-1,4 aminocycloalkenol products were obtained. We anticipate that this new aromatic substitution/coupling protocol will be of considerable utility.

Acknowledgment. We thank the Lizzadro Magnetic Resonance Research Center at Notre Dame for NMR facilities and Nonka Sevova for mass spectroscopic analyses. We acknowledge The University of Notre Dame and NIH (GM 07855) for support of this research.

Supporting Information Available: General method, experimental details, ^{1}H NMR and ^{13}C NMR spectra for **1d**, **4a**, **4b**,**c**, **4f**, **5b**−**j**, **6**, **10**, **12**, and **13**, and COSY and HSQC spectra for **4b** and **5b**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9027607