

Published on Web 10/05/2005

## Synthesis of Dihydronaphthalenes via Aryne Diels-Alder Reactions: Scope and Diastereoselectivity

Chris Dockendorff, Stefan Sahli, Madeline Olsen, Ludovic Milhau, and Mark Lautens\*

Davenport Laboratories, Department of Chemistry, University of Toronto, Toronto, Ontario, Canada M5S 3H6

Received August 11, 2005; E-mail: mlautens@chem.utoronto.ca

We have been developing approaches to hydronaphthalenes using various stereo- and enantioselective ring-opening procedures. A number of useful transformations have emerged but most are best suited to preparing 1,2-substituted analogues.<sup>1</sup> The need for methods that directly form 1,4-substitution patterns is related to the diverse biological activity observed with this "privileged" structural class. Some methods are known,<sup>2–4</sup> but simpler approaches are of interest. A very attractive strategy is the Diels—Alder reaction between an aryne (dehydrobenzene)<sup>5</sup> and an acyclic diene (Scheme 1), but the

Scheme 1. Aryne Diels-Alder Reaction with Acyclic Dienes



scope and utility of this approach have not been investigated in depth since the first report by Wittig in the 1960s.<sup>6</sup> Aryne Diels– Alder (ADA) reactions with cyclic dienes are frequently utilized; however, reactions with functionalized acyclic dienes are much less common.<sup>7</sup> A method leading to substituted 1,4-dihydronaphthalenes would be highly desirable, especially if at least one of the substituents could be a heteroatom or an easily manipulated functional group. We now report a direct and stereoselective route to *cis*-substituted dihydronaphthalenes via ADA reactions with acyclic dienes and demonstrate the utility of the products with a short synthesis of sertraline.

We began our study by reacting various acyclic 1,3-dienes with benzyne generated from benzenediazonium-2-carboxylate (BDC) using Friedman's procedure.<sup>8</sup> Ethyl sorbate **1a** (1.2 equiv) and BDC in 1,2-dichloroethane (DCE) at 60 °C gave the desired cycloadduct **2a** cleanly by NMR (crude yield 60%). However, **2a** and the excess ethyl sorbate were inseparable by TLC and column chromatography. We repeated the reaction using ethyl sorbate as the limiting reagent with a slurry of an excess (~2 equiv) of BDC in DCE at 60 °C to provide **2a** in 74% yield.<sup>9-11</sup> Several other benzyne generation methods were also investigated, all of which gave inferior results.<sup>9</sup>

We prepared a collection of functionalized dienes<sup>9</sup> for screening in the Diels–Alder reaction with benzyne (Table 1). Carbonylsubstituted dienes were used since these are easy to synthesize via Horner–Emmons–Wadsworth reactions. We observed that the cycloaddition yields were consistently good, which is noteworthy considering that reactions of *cyclic* dienes under similar conditions with benzyne usually gave yields <70%. Dienyl esters and amides (**1h**) gave clean reactions; however, dienyl acid **1e** gave a complex mixture, perhaps due to insertion into the O–H bond.<sup>5</sup> Aryl substituents with both electron-withdrawing and electron-donating groups are tolerated (**1c**–**f**), except that the strongly electrondonating dimethylamino group gave no trace of cycloadduct (**1g**). The reaction can also proceed with some trisubstituted dienes. An electron-withdrawing ester group in the 3-position gave quantitative

Table 1. Cycloadditions with Carbonyi-Substituted Dienes					
ĺ	$CO_2^{-}$ +		►, 60°C 2 M		x L Y
	1a-k			2a-k	
diene	R	Х	Y	product	yield <sup>b</sup> (%)
1a	Me	OEt	Н	2a	74
1b	Ph	OEt	Н	2b	84
1c	3,4-ClPh	OEt	Н	2c	86
1d	3,4-ClPh	OBn	Н	2d	78
1e	3,4-ClPh	OH	Н	2e	$(50)^{c}$
1f	4-(MeO)Ph	OEt	Н	2f	75
1g	4-(Me <sub>2</sub> N)Ph	OEt	Н	2g	$(0)^{d}$
1h	Ph	$N(i-Pr)_2$	Н	2h	54
1i	Ph	OMe	Me	2i	$(0)^{e}$
1j	Ph	OEt	Br	2j	80
1k	Ph	OMe	CO <sub>2</sub> Et	2k	85 <sup>f</sup>

4. Outline difference of the Oracle and Oracle of the test Diseases

<sup>*a*</sup> All reactions were performed according to the optimized conditions detailed in the Supporting Information. <sup>*b*</sup> Isolated yield (NMR yield with acetone or dichloromethane as standard is in parentheses). Unless otherwise noted, all diene starting material was consumed. <sup>*c*</sup> Complex mixture. <sup>*d*</sup> No reaction. <sup>*e*</sup> No reaction, <sup>*c*</sup> Ut diene was consumed. <sup>*f*</sup> Isomerization of the product occurred with flash chromatography.

yields by NMR (1k), though the product was unstable to column chromatography with silica gel. A diene with a methyl group in the 3-position (1i) was consumed in the reaction but gave no desired product by NMR.<sup>12</sup> The best result was obtained with a bromo group (1j), which gave the product in 80% isolated yield. The expected *cis* stereochemistry from a concerted [4+2] process was confirmed by an X-ray structure of product 2h.<sup>9</sup>

Cycloadditions with NC-, NO<sub>2</sub>-, and O-substituted dienes are also possible.<sup>9</sup> Particularly with O-substituted diene **3**, the ADA reaction proceeds efficiently under the standard conditions with BDC to generate **4** in 77% yield,<sup>13</sup> or alternatively with benzyne generated from 2-(trimethylsilyl)phenyl triflate and CsF in CH<sub>3</sub>-CN (Scheme 2).<sup>14</sup>

Scheme 2. Cycloaddition with Heterosubstituted Diene



We have also adapted the ADA reaction to the preparation of enantiomerically enriched products. Our first approach was to attach a chiral auxiliary to a diene carbonyl group. Poor to moderate diastereoselectivities (1:1 to 3.5:1) were obtained using several different auxiliaries under our standard conditions with BDC. However, excellent diastereoselectivities (>19:1) are obtained with Table 2. Highly Diastereoselective Aryne Cycloadditions TfC CsF (6 equiv)  $\cap$ CH<sub>2</sub>CN rt TMS 3 equiv dr >19:1 1 eauiv Ř 2I-2p 11-10 diene R Х Υ product yield (%) 11 Me Η Η 21 60 48 1m Ph н Η 2m 3,4-ClPh Η Η 40 1n 2n 3,4,5-(MeO)Ph Н 45 Н 20 10 11 Me -OCH<sub>2</sub>O-2p 51

Oppolzer's sultam, specifically when using benzyne generated from 2-(trimethylsilyl)phenyl triflate and CsF in CH<sub>3</sub>CN (Table 2). The assignment of the diastereomers **2l** and **2m** is based upon ROESY NMR measurements. In addition, this method was successfully extended to cycloadditions with substituted arynes (**2p**, Table 2).

To demonstrate the utility of the alkoxycarbonyl-substituted 1,4dihydronaphthalenes as precursors to medicinally important products, a Curtius rearrangement was utilized as a key step in a synthesis of racemic sertraline<sup>15</sup> (Scheme 3). Moreover, **2n**, which

## Scheme 3. Synthesis of Sertraline



is obtained almost diastereomerically pure in 40% (unoptimized) yield, is a precursor for the corresponding asymmetric synthesis.

The Diels–Alder reaction between benzyne and dienyl ester **1d** proceeded in good yield using the standard protocol. Cycloadduct **2d** was hydrogenated and deprotected in one pot without epimerization or loss of the aryl chlorides to give acid **5**. The benzyl ester was essential, since the analogous ethyl ester could not be hydrolyzed under basic conditions (KOH, THF/water, 60 °C; K<sub>2</sub>-CO<sub>3</sub>, MeOH/water, room temperature) without epimerization of the sensitive benzylic center alpha to the carbonyl group.

The Curtius rearrangement of **5** was best conducted by formation of the acyl azide (DPPA or ClCO<sub>2</sub>Et followed by NaN<sub>3</sub>) and then slow addition to a hot solution (90 °C) of allyl alcohol in toluene. Allyl carbamate **6** was isolated in 65% yield and subsequently N-methylated and deprotected with a water-soluble Pd(0) catalyst<sup>16</sup> to give sertraline, with NMR spectrum consistent with that reported by workers at Pfizer.<sup>17</sup>

In conclusion, we have reported that the aryne Diels-Alder reaction with acyclic dienes is a useful method for the synthesis of functionalized 1,4-dihydronaphthalenes. Reactions with electron-withdrawing substituents on the diene generally proceed favorably, indicating that an inverse electron-demand Diels-Alder pathway might be operating in these cases. The first diastereoselective aryne Diels-Alder reaction to provide enantiomerically enriched cy-cloadducts was developed.

Acknowledgment. We thank AZRCM, NSERC, the ORDCF, and the University of Toronto for funding of this research. C.D. thanks the W. C. Sumner Foundation for a postgraduate fellowship. S.S. thanks the Swiss National Science Foundation for a postdoctoral fellowship. L.M. thanks IUT Castres for an exchange visit to Toronto. We also thank Dr. Alex Young for MS analysis, Dr. Alan Lough for X-ray analysis, Dr. Tim Burrow for assistance with NMR instruments, and Perkin-Elmer Canada for lending us an Isco Companion automated chromatography system.

**Supporting Information Available:** Experimental procedures, additional data tables, characterization data, and <sup>1</sup>H and <sup>13</sup>C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

## References

- See for example: (a) Lautens, M.; Fagnou, K.; Hiebert, S. Acc. Chem. Res. 2003, 36, 48 and references therein. (b) Lautens, M.; Fagnou, K.; Yang, D. J. Am. Chem. Soc. 2003, 125, 14884. (c) Lautens, M.; Dockendorff, C. Org. Lett. 2003, 5, 3695.
- (2) Via dissolving metal reductions: (a) See for example: Rabideau, P. W.; Husted, C. A.; Young, D. M. J. Org. Chem. 1983, 48, 4149. (b) For a review, see: Rabideau, P. W.; Marcinow, Z. Organic Reactions; John Wiley and Sons Inc.: New York, 1992; Vol. 42.
- (3) Via Os- and Re-mediated sequential addition of electrophiles and nucleophiles to naphthalene: (a) Harman, W. D.; Winemiller, M. D. J. Am. Chem. Soc. 1998, 120, 7835. (b) Harman, W. D.; Ding, F.; Valahovic, M. T.; Keane, J. M.; Anstey, M. R.; Sabat, M.; Trindle, C. O. J. Org. Chem. 2004, 69, 2257 and references therein.
- (4) Via Diels-Alder reactions between alkynes and *o*-quinone dimethides; see for example: Danishefsky, S. J.; Allen, J. G.; Hentemann, M. F. J. Am. Chem. Soc. 2000, 122, 571.
- (5) Recent reviews on arynes: (a) Pellissier, H.; Santelli, M. *Tetrahedron* 2003, 59, 701. (b) Wenk, H. H.; Winkler, M.; Sander, W. *Angew. Chem.*, *Int. Ed.* 2003, 42, 502.
- (6) Wittig, G.; Dürr, H. Justus Liebigs Ann. Chem. 1964, 672, 55.
- (7) Some of the few synthetically useful intermolecular examples: (a) Jones, M.; Levin, R. H. J. Am. Chem. Soc. **1969**, 91, 6411. (b) Angerbauer, R.; Schmidt, R. Angew. Chem., Int. Ed. Engl. **1979**, 18, 304. For a recent intramolecular example, see: (c) Hayes, M. E.; Shinokubo, H.; Danheiser, R. L. Org. Lett. **2005**, 7, 3917.
- (8) Logullo, F. M.; Seitz, A. H.; Friedman, L. Org. Synth. 1968, 48, 12.
- (9) See Supporting Information for details.
- (10) DCE was previously reported to be a preferred solvent for the generation of benzyne from BDC: Heaney, H.; Buxton, P. C.; Fensome, M.; Mason, K. G. *Tetrahedron* **1995**, *51*, 2959.
- (11) The addition of a catalytic amount of BHT as a radical inhibitor gave no improvement in the yield.
- (12) This substrate may be prone to, e.g., an ene reaction, which could lead to a complex mixture of products. See for example ref 6.
- (13) Cycloadduct 4 is made as mixture of diastereomers ( $\sim$ 2:1).
- (14) We were inspired to try these conditions by a recent report by Mori and co-workers: Sato, Y.; Tamura, T.; Mori, M. Angew. Chem., Int. Ed. 2004, 43, 2436.
- (15) For recent industrially relevant syntheses of sertraline, see for example: (a) Vukics, K.; Fodor, T.; Fischer, J.; Fellegvári, I.; Lévai, S. Org. Process Res. Dev. 2002, 6, 82. (b) Colberg, J. C.; Taber, G.; Pfisterer, D. M. Org. Process Res. Dev. 2004, 8, 385.
- (16) Genêt, J. P.; Lemaire-Audoire, S.; Savignac, M.; Blart, E.; Bernard, J.-M. Tetrahedron Lett. 1997, 2955.
- (17) DeNinno, M. P.; Eller, C.; Etienne, J. B. J. Org. Chem. 2001, 66, 6988.

JA055498P