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A novel α,β -unsaturated nitron-aryne [3+2] cycloaddition and its application in the synthesis of the cortistatin core

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Abstract

We describe here a novel α,β -unsaturated nitron-aryne [3+2] cycloaddition. The resulting benzoisoxazolines underwent N-O bond reduction–elimination–electrocyclization sequence to furnish a variety of polysubstituted 2*H* or 2-alkylated-1-benzo-pyrans. The application of this methodology was further demonstrated in the synthesis of the oxa[3.2.1]octene moiety of cortistatin A.

As described in the previous communication, we have been pursuing a total synthesis of cortistatin A (**1**) in the context of an aggressive program directed to the discovery of even more valuable cortistatin analogs. Isolated by Kobayashi and co-workers,¹ cortistatin A has received a great deal of attention from the synthetic community, due to its promising biological activity and unusual structural features.² These efforts culminated in the first synthesis of cortistatin A by Baran and co-workers.³ A total synthesis of **1** was recently accomplished by the Nicolaou group.⁴ In designing a synthetic strategy toward **1** that would be amenable to a program of diverted total synthesis,⁵ we envisioned an intermediate of the type **8** to be a key launching point, from which we could prepare a range of cortistatin analogs.⁶ In the preceding communication, we demonstrated an efficient route to the cortistatin pentacyclic core via a Snieckus reaction and subsequent Masamune alkylation.⁷ Herein, we explore a very different approach to compound **7**.

As shown in Scheme 1, we envisioned employing a defining 1,3-dipolar cycloaddition reaction⁸ between generic aryne **2** and α,β -unsaturated nitron **3**, to generate benzoisoxazoline **4**. The latter would be advanced to the desired benzopyran **7** through sequential reductive N–O bond cleavage, 1,4-elimination, and 6 π -electrocyclization. Finally, Masamune alkylation of **7** would afford intermediate **8**. Interestingly, there is little precedent for the type of [3+2] cycloaddition proposed herein (**2** + **3** $\rightarrow$ **4**). To the best of our knowledge, only one example of an α,β -unsaturated nitron-aryne [3+2] cycloaddition⁹ has been reported. Furthermore, there are a paucity of examples of even simple nitron-aryne [3+2] cycloadditions.¹⁰

Recognizing the potential general applicability of this type of reaction to the synthesis of complex molecules, and hoping to apply this general strategy to the synthesis of cortistatin A,

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we sought to develop and optimize a generally useful α,β -unsaturated nitron-aryne [3+2] cycloaddition protocol.

Our initial investigations focused on the sterically unencumbered nitron substrates **9a–c** and the benzyne derived from 2-bromophenyl triflate **10**. The α,β -unsaturated nitrones were prepared from the corresponding α,β -unsaturated aldehydes by treatment with alkylated hydroxylamine (see Supporting Information for details). As shown in Table 1, when a solution of α,β -unsaturated nitron **9a** and 2-bromophenyl triflate **10** was treated with *n*BuLi at -78°C , the desired benzoisoxazoline **11a** was isolated in moderate to good yields, with recycling of starting material **9a** (entry 1–4). The best yield (74%) was observed when a 1:2 ratio of **9a:10** was employed (entry 4). In this case, the reaction was complete within 5 minutes, and longer reaction times did not lead to improvements in yield. Methylated (**9b**) and benzylated (**9c**) nitrones gave significantly lower reaction yields in comparison to the *t*Bu nitron (**9a**), presumably due to acidic protons located α to the nitrogen center (entries 5 and 6).

With these improved conditions in hand, we sought to probe the generality of the reaction with respect to the nature of the bromoaryl triflate component (see Supporting Information for synthetic details). As shown in Table 2, the reaction is capable of efficiently accommodating a range of functionalities. While all reactions proceeded in moderate to good yield, we did observe poor product regioselectivities when 2-bromo-4-methoxyphenyl triflate **12b** or 1-bromonaphthalen-2-yl triflate **12c** were used (entries 2 and 3). These findings were not unexpected, since the conjugation effect does not influence the electronic properties of the aryne's reactive orbitals, due to their perpendicular relationship to the aryl π -electron system. Based on this theory, electron withdrawing or electron donating groups *ortho* to the aryne could polarize the frontier orbital of the aryne dipolarophile, and therefore help to control the regioselectivity. Steric factors must also be taken into account. In fact, when 2-iodo-3-methoxyphenyl triflate **12d** was used, only product **13d** was obtained, in 74% yield. The structure of **13d** was unambiguously verified by X-ray crystallography.¹¹ The electron donating –TMS group (**12e**) served to completely invert the regioselectivity, furnishing **13e** as the only cycloadduct in modest yield (41%).

We next prepared a range of α,β -unsaturated nitron substrates. Nitrones **14a–c** were combined with **10**, under standard reaction conditions. Each substrate smoothly underwent cycloaddition to furnish products **15a–c** in good yield (Table 3). However, almost no stereoselectivity was observed with nitrones **14a** and **14b**, presumably reflecting the remoteness of the resident stereocenter. We note that the lack of stereocontrol observed in these cases will not permanently impact our own synthetic efforts toward cortistatin A, since our strategy calls for the elimination of the newly generated stereocenter in subsequent steps.

Having established the substrate scope of the 1,3-dipolar cycloaddition between α,β -unsaturated nitrones and arynes, we now sought to develop an efficient protocol by which to convert the cycloadduct to a compound of the general type **16** (Table 4). First, reductive cleavage of the N–O bond was accomplished through exposure to Zn/AcOH. The resulting amino-phenol was heated in toluene. The hoped-for 1,4-elimination of the amino group proceeded smoothly, presumably assisted by intramolecular deprotonation of the phenol by the secondary amine. The quinomethide seemingly underwent spontaneous 6π -electrocyclization to furnish the desired compound **16**. It is worth noting that in generating the quinomethide, it is not necessary to activate the leaving group (for instance, through pre-formation of a quaternary ammonium salt).¹²

As shown in Table 4, a number of benzoisoxazolines were subjected to the reduction–elimination–electrocyclization sequence. All substrates underwent the sequence in good to excellent overall yield (entries 1–6). The *tert*-butylated benzoisoxazoline (**11a**) again proved

superior to the methylated (**11b**) and benzylated (**11c**) substrates (entry 1). When the 1.4:1 diastereomeric mixture of **15a** was subjected to the reaction sequence, the product, **16e**, was obtained with enhanced stereoselectivity (8:1) (entry 5). The predominant isomer was the thermodynamically favored product, in which the isopropenyl group is situated in the equatorial position. Interestingly, NMR monitoring of the elimination-electrocyclization sequence revealed the reaction itself to be complete within 1h, although adduct was observed with no diastereoselectivity. Prolonged heating yielded higher diastereoselectivities, with the highest selectivity (12:1) observed after 18h of heating (see Supporting Information for details). A similar result was observed in the transformation of **15b** to **16f** (entry 6).

Having developed an efficient cycloaddition/cyclization protocol, we now explored the application of the method to the synthesis of the core structure of cortistatin A. Intermediate **23** was selected as a model system. As outlined in Scheme 2, aldehyde **17** was converted to nitron **18**. Next, 1,3-dipolar cycloaddition between **18** and the aryne generated from **19**¹³ provided benzoisoxazoline **20**, which was submitted to the standard reduction–elimination–electrocyclization sequence to afford **21** in 55% overall yield from **18**. Alcohol deprotection, followed by bromination, gave compound **22**, which, upon exposure to TBAF, readily underwent cyclization to provide the target intermediate, **23**.¹⁴

In summary, a general method for the 1,3-dipolar cyclization between α,β -unsaturated nitrones and arynes has been developed. In addition, a highly efficient N–O bond reduction–elimination–electrocyclization sequence furnishes polysubstituted 2*H* or 2-alkylated-1-benzopyrans. Finally, Masamune alkylation has been used to synthesize the oxa[3.2.1]octene moiety of cortistatin A.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1. Proposed nitron-aryne [3+2] cycloaddition en route to cortistatin A (**1**).

Scheme 2.

Synthesis of the core structure (**23**) of cortistatin A. a) *t*-BuNHOH-HOAc, TEA, CH₂Cl₂, RT, 6 days, 98%; b) *n*-BuLi, THF, 2 h; c) Zn, HOAc, RT, overnight; 170 °C, toluene, overnight, 55% from **18**; d) Me₂BBr, *i*-Pr₂NEt, anisole, CH₂Cl₂, -78 °C, 20 min, 84%; e) CBr₄, PPh₃, CH₂Cl₂, 1 h, 87%; f) TBAF, THF, r.t., 5 min, then 50 °C, 20 min or RT, 2 days, 52%.

Table 1^aCycloaddition of α,β -unsaturated aldehydes (**9**) with arynes (**10**).

entry	–R	ratio 9:10	yield (11)	RSM (9)
1	– <i>t</i> Bu (9a)	2:1	49% (11a)	54%
2	– <i>t</i> Bu (9a)	1:1	47% (11a)	28%
3	– <i>t</i> Bu (9a)	1:1.2	51% (11a)	37%
4	– <i>t</i> Bu (9a)	1:2	74% (11a)	10%
5	–Me (9b)	1:2	50% (11b)	ND
6	–Bn (9c)	1:2	38% (11c)	ND

^a Cycloaddition reaction condition optimization: To a solution of **9** and **10** in THF at –78 °C was added *n*BuLi (1 eq. to **10**). After workup, product **11** was purified by silica gel chromatography. RSM: recycled starting material (**9**); ND: not determined.

Table 2

Substrate scope of aryne component (**12**).

entry	substrate (12)	product (13)	yield (%)
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1

entry	substrate (12)	product (13)	yield (%)
2	<p>12b</p>	<p>13b (1.5:1)</p>	88
3	<p>12c</p>	<p>13c (1.7:1)</p>	70

entry	substrate (12)	product (13)	yield (%)
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4

5

Substrate scope of nitrono component (**14**).

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entry

nitronium (14)

2

entry

nitronium (14)

3

Table 4

Reduction–Elimination–Electrocyclization Sequence.

entry	substrate
1	11a ($R^3 = tBu$) 11b ($R^3 = Me$) 11c ($R^3 = Bn$)

entry

substrate

2

entry

substrate

3

entry

substrate

4

entry

substrate

5

6