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An Enamide-Benzyne-[2 + 2] Cycloaddition: Stereoselective Tandem [2 + 2]–Pericyclic Ring-Opening–Intramolecular *N*-Tethered [4 + 2] Cycloadditions

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Abstract

Benzyne-[2 + 2] cycloadditions with enamides are described. This effort led to the development of a highly stereoselective tandem [2 + 2] cycloaddition–pericyclic ring-opening–intramolecular-*N*-tethered- [4 + 2] cycloaddition for rapid assembly of nitrogen heterocycles.

Chemistry of benzyne¹ has reemerged as evident by an elegant array of work that has appeared in the recent literature covering a number of different synthetic transformations.^{2–4} As Larock^{4g} pointed out, this new surge is in part related to the usage of Kobayashi's⁵ mild fluoride-based conditions for generating benzyne *in situ* from *ortho*-(trimethylsilyl)aryl triflates. In particular, Stoltz's⁶ beautiful studies on annulations of enamides with benzyne en route to indolines and iso-quinolines provoked us to envision another transformation also involving enamides but through a [2 + 2] cycloaddition as shown in Scheme 1. While benzyne-[2 + 2] cycloaddition is well-known,^{1,7} there are very few examples involving enamines⁸ with no systematic examinations of enamides in this capacity.^{1,9,10} While conceptually simple, this endeavor is timely and significant because enamides represents an increasingly more accessible substrate^{11–14} and a useful functional group in modern organic synthesis.^{15,16}

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Supporting Information **Available:** Experimental procedures as well as NMR spectra and characterizations are available for all new compounds and free of charge via Internet <http://pubs.acs.org>.

More importantly, we recognized that the union of benzyne and enamides would lead to not only amido-benzocyclobutanes **1**, which are excellent precursors to amido-*o*-quinonedimethides **2** [or a 1-amidodiene]^{17,18} through pericyclic ring-opening,^{1,19} but also the possibility of a tandem sequence consisting of benzyne-[2 + 2] cycloaddition–ring-opening–*N*-tethered intramolecular [4 + 2] cycloaddition.^{1,19,20} This tandem process should be useful for rapid assembly of complex nitrogen heterocycles [(benzyne+enamide)→**1a**→**2a**→**3**]. We communicate here our success in this endeavor.

Feasibility of the enamide-benzyne [2 + 2] cycloaddition was established using benzyne precursor **4** and enamide **5** in the presence of a fluoride source [Table 1]. The first fluoride anion source employed was TBAT [tetra-*n*-Bu-ammonium triphenyl-difluorosilicate]. After screening through a variety of solvents, 1,4-dioxane proves to be the optimal solvent [entries 6 and 7], leading to amido-benzocyclobutane **6**²¹ in 83% yield. Intriguingly, THF, the commonly used solvent for benzyne reactions, afforded the desired product in only 14% isolated yield [entry 1] with the formation of a significant side product.²² Increasing the loading of silylaryl triflate **4** and fluorideion afforded higher yields [entry 6 versus 7]. When examining other fluoride sources [entries 8–10], none was effective except CsF, which was ultimately determined to be the best fluoride source for ease of operation [entry 10].

Having established these conditions, a variety of enamides were found to undergo the benzyne-[2 + 2] cycloaddition [Table 2]. Electronically, cycloadditions of both *N*-acyl and *N*-sulfonyl enamides **7** and **9** proceeded well [entries 1–2]. Cyclic enamides **11a** and **11b** were also excellent substrates, affording unique *aza*-tricycles **12a** and **12b**, respectively, in nearly quantitative yields [entries 3–4]. In addition, achiral oxazolidinone substituted enamide **13a** was viable for the cycloaddition, leading to amido-benzocyclobutane **14a** in 62% yield [entry 5], while chiral enamides **13b–e** were equally efficient [entries 7–11]. It is noteworthy that amido-benzocyclobutane product **14e** provides an access to free amino-benzocyclobutane via reductive ring-opening of the chiral oxazolidinone motif through hydrogenolysis.²³

Although amido-benzocyclobutane products **14b–e** were isolated as an inseparable mixture of diastereomers with ratios of 1:1 to 2:1, to control this diastereoselectivity is not essential because the major application of these amido-benzocyclobutanes pertains to a pericyclic ring-opening, which would lose the stereochemical information en route to amido-*o*-quinonedimethides. In accord with this understanding, we recognized that while these new amido-benzocyclobutanes are synthetically useful, the most attractive feature here is to employ enamide-benzyne-[2 + 2] cycloaddition in tandem with the ring-opening to *o*-quinonedimethide for the ensuing [4 + 2] cycloaddition.

As shown in Scheme 2, this concept was readily achieved using enamide **15** tethered with an olefin to give *aza*-tricycle **19** in 95% yield as a single diastereomer [assigned via nOe experiments]. *Aza*-tricycle **22** could also be obtained from the respective enamide **20**. The formation of **19** [or **22**] would constitute a four-bond formation through benzocyclobutane synthesis [2 red bonds], a torquoselective pericyclic ring-opening in favor of the amido group rotating outwardly^{24,25} and an *N*-tethered intramolecular [4 + 2] cycloaddition. The latter two reactions in tandem already represents a highly useful synthetic strategy, as evident from elegant work by Oppolzer²⁰, thereby further accentuating the potential significance of developing an enamide-benzyne-[2 + 2] cycloaddition manifold.

The synthetic scope of this tandem process can be illustrated in two facets. Firstly, as shown in Scheme 3, cycloadditions of enamides **23a** and **23b** tethered to a *cis*-olefin gave respective cycloadducts **26a** and **26b** in good yields as a single isomer with all *cis* relative stereochemistry at C α , C β , and C γ as assigned through nOe experiments. The *cis* relative stereochemistry at C β and C γ suggests the concerted nature in the [4 + 2] cycloaddition, as the integrity of the

olefin geometry is preserved.^{1,19} In addition, enamide **27** with a tri-substituted olefin was also feasible for the tandem sequence, although the yield for the desired *aza*-tetracycle **28** is lower. We note here that even with the more electron-rich di- and tri-substituted olefins, the benzyne-[2 + 2] cycloaddition still favored the enamide motif.

The second facet features an asymmetric variant of this tandem sequence [Scheme 4]. Chiral enamide **29**, derived from (*S*)-aspartic acid, could be transformed into enamide **31** tethered to a *trans*-acrylate motif through Swern oxidation and Wittig olefination. Subjecting **31** to the tandem benzyne-[2 + 2]-ring-opening-intramolecular [4 + 2] process afforded *aza*-tetracycle **34** in a highly stereoselective manner. This exercise underscores the timeliness and significance of this strategy because chiral enamides are readily accessible through the current state of art in their preparations. In addition, the robustness of enamides allows one to carry them through multiple organic transformations as a functional group while assembling greater complexity.

We have described here an enamide-benzyne-[2 + 2] cycloaddition. This work led to the development of a highly stereoselective tandem [2 + 2] cycloaddition-pericyclic ring-opening-intramolecular [4 + 2] cycloaddition that should be useful for the rapid construction of nitrogen heterocycles. Efforts in applying this tandem process to alkaloid synthesis are currently underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.

A Tandem Benzyne-Enamide-[2 + 2]-Diels-Alder.

Scheme 2.
A Tandem Benzyne-Enamide-[2 + 2]-[4 + 2].

Scheme 3.
 Substituted Olefins for [4 + 2] Cycloaddition.

Scheme 4.
An Asymmetric Tandem $[2 + 2]$ – $[4 + 2]$.

Table 1

Fluoride Sources and Solvents for Benzyne Formation.

entry	4 [equiv]	F [⊖] [equiv] ^a	solvent ^b	time [h]	yield [%]: NMR	isolated
1	2.0	TBAT [2.0]	THF	6	-	14
2	2.0	TBAT [2.0]	CH ₃ CN	22	-	-
3	2.0	TBAT [2.0]	toluene	22	29	-
4	2.0	TBAT [2.0]	ClCH ₂ CH ₂ Cl	22	-	-
5	4.0	TBAT [4.0]	DME	12	51	-
6	2.0	TBAT [2.0]	dioxane	22	41	-
7	4.0	TBAT [4.0]	dioxane	12	71	83
8	3.0	HF-pyridine	dioxane	22	-	-
9	3.0	TBAF [4.0]	dioxane	22	-	-
10	3.0	CsF [4.0]	dioxane	22	-	87

^aTBAT: Tetra-*n*-butyl-ammonium triphenyldifluorosilicate.

^bDME: Dimethoxyethane; dioxane: 1,4-dioxane.

Table 2

A General Benzyne-Enamide-[2 + 2] Cycloaddition.

entry	enamides ^a	
1		7
2		9
3		
4		11a: n = 1 11b: n = 0

entry	enamides ^a
5	<p>13a: R = H 13b: R = Ph 13c: R = Bn</p>
6	
7	
8	<p>13d</p>
9	<p>13e</p>

^aUnless otherwise noted, all reactions were carried out in 1,4-dioxane at 110 °C with CsF (4.0 equiv) and **4** (3 equiv) being employed.

^bIsolated yields.

^c*Dr* ratio is 2:1 as determined by ¹H-NMR; major isomer unassigned.

^d*Dr* ratio is 1:1 as determined by ¹H-NMR.