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SmI_2-Mediated Coupling of Nitrones and *tert*-Butanesulfinyl Imines with Allenoates: Synthesis of β-Methylenyl-γ-lactams and Tetramic Acids

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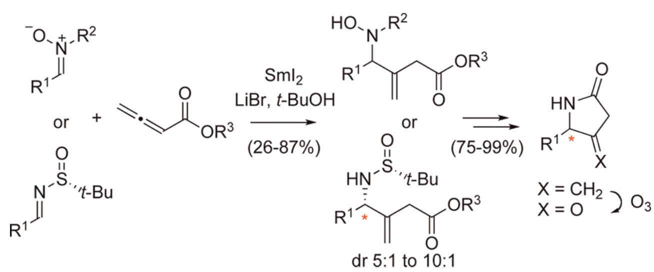
ABSTRACT



Nitrones and *tert*-butanesulfinyl imines undergo conjugate addition to alkyl allenoates under SmI_2-mediated reductive coupling conditions to produce novel β-methylenyl-substituted γ-amino esters. The latter were readily transformed into the corresponding β-methylenyl-γ-lactams by simple zinc reduction (*N*-hydroxy amines) or by acid hydrolysis (sulfinamides). The diastereoselective preparation of various β-methylenyl-γ-lactams offers a route to tetramic acids, the key structural features of an important class of bioactive natural products.

The development of reactions involving samarium diiodide is unceasingly a topic of interest in synthetic chemistry, in large part because this mild reducing agent allows the selective creation of C–C bonds from various organic functional groups.[1] In recent years, the SmI_2-mediated cross-coupling reactions of nitrones[2] sulfinyl imines[3] and other iminium equivalents[4] with acrylic esters and amides have been developed for the synthesis of γ-amino acid derivatives, including γ-lactams. With these precedents, the SmI_2-mediated reductive cross-coupling of nitrones **1** or sulfinylimines **2** with allenoates **3**,[5] possibly yielding β-methylenyl-γ-amino acid derivatives **4**, was anticipated (Scheme 1).

Synthetic methods to prepare compounds **4** are scarce. They usually involve the addition of amidomalonate[6] or glycinate[7] anions to allenoates and, thus, are limited to the

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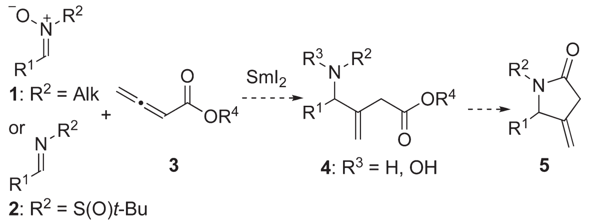
Scheme 1. General Approach

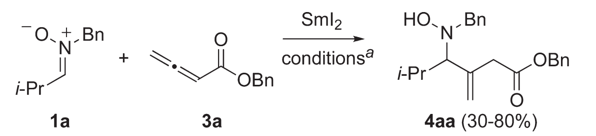


preparation of glutamic acid derivatives ($R^1 = CO_2R$). A method to prepare a large variety of compounds **4** would therefore be useful, especially since they might serve as precursors of *β*-methylenyl-*γ*-lactams **5**, themselves being potential intermediates for the synthesis of tetramic acids.[8] Published approaches for the construction of *β*-methylenyl-*γ*-lactams include radical cyclization of propargyl bromoamides in the presence of Bu_3SnH and AIBN,[9] MgI_2-promoted ring expansion of secondary methylenecyclopropyl amides,[10] and indium-catalyzed Conia-ene reactions.[11] Alternative synthetic routes to **5**, however, remain highly desirable.

Nitrones are known to react with activated allenes under thermal conditions to produce cycloadducts which can rearrange to give pyrrolidin-3-ones.[12] We assumed that SmI_2-promoted reductive coupling of nitrones and allenoates would manifest a complementary pattern of reactivity, giving access to 4-methylenyl-5-substituted-pyrrolidin-2-ones (**5**).

Nitrone **1a**[13] and allenoate **3a**[14] (1.4 equiv) were first treated at −78 °C with 3 equiv of SmI_2 in the presence of water, conditions previously described for the reductive coupling of nitrones with acrylic esters (Scheme 2).[2a,e] The expected *N*-hydroxyamine **4aa** was formed, although in a disappointing 30% yield; nitrone **1a** was recovered (44%), along with benzyl but-3-enoate (**6a**),[15] resulting from the reduction of allenoate **3a** by SmI_2.[16] A screening of conditions was next carried out in the presence of various additives,[17] in an attempt to favor the desired cross-coupling of allenoate **3a** with nitrone **1a** rather than its competitive conjugate reduction.[18] In light of the work of Ellman,[3] we next introduced 12 equiv of this salt[19] in the reaction mixture: the yield of **4aa** was increased to 49%, but compound **6a** was still a major side product. The use of a noncoordinating source of protons instead of water was also found to be beneficial to increase the yield in **4aa** up to 60%.[20] It was finally found that better yields of the desired product **4aa** could be obtained by iterative introduction of excess allenoate and SmI_2 to limit the formation of **6a**.

Scheme 2. SmI_2-Mediated Cross-Coupling of **1a** and **3a**



[a] See Supporting Information for the conditions screened.

Optimal conditions consisted in treating a mixture of nitrone **1a**, 1.4 equiv of allenoate **3a**, 3.5 equiv of *tert*-butanol, and 12 equiv of LiBr at −40 °C with 3 equiv of SmI_2, again after 30 min with additional 0.6 equiv of allenoate and 1 equiv of SmI_2, and once more, after 30 min with another 0.5 equiv of allenoate and 0.5 equiv of SmI_2. After 3 h, consumption of nitrone **1a** was almost complete and

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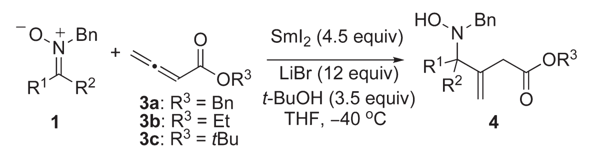
the desired N-hydroxyamine **4aa** could be isolated in 80% yield.

Using these conditions, the scope of the reaction was next evaluated. With benzyl buta-2,3-dienoate (**3a**) as the allenic partner, in most of the cases the expected N-hydroxyamines **4** were obtained in good yields (Table 1, entries 1–6). However, compounds **4ga** and **4ha** (Table 1, entries 7 and 8) were formed in only 44% and 26% yield, respectively, a decrease probably due to steric hindrance. The nature of the ester group also seemed to play a role in the efficiency of the process as *tert*-butyl ester **3c** did not couple with nitrones as efficiently as its benzyl (**3a**) or ethyl (**3b**) analogues (Table 1, entries 1, 3 and 9–11).

Table 1. Cross-Coupling of Nitrones **1a–h** with Allenoates **3a–c**



entry	R^1	R^2	R^3	product	% yield (% recovered nitrone **1**)
1	*i*-Pr	H	Bn	**4aa**	80 (16)
2	Me	H	Bn	**4ba**	68 (31)
3	Et	H	Bn	**4ca**	74 (23)
4	*i*-Bu	H	Bn	**4da**	71 (29)
5	*c*-Hex	H	Bn	**4ea**	62 (31)
6	*c*-Pr	H	Bn	**4fa**	56 (43)
7	*t*-Bu	H	Bn	**4ga**	44 (52)
8	$(-CH_2-)_5$		Bn	**4ha**	26 (30)
9	*i*-Pr	H	Et	**4ab**	64 (33)
10	*i*-Pr	H	*t*-Bu	**4ac**	32 (52)
11	Et	H	*t*-Bu	**4cc**	36 (ND)

The effect of an α- or γ-substituent in the allenoate partner was also investigated. When ethyl 2-methylbuta-2,3-dienoate (**7**) was treated with nitrone **1a** under the cross-coupling conditions, the coupling product **8** was isolated in 40% yield, as a 2:1 mixture of diastereomers, along with 46% of recovered nitrone **1a** (Scheme 3). The γ,γ-disubstituted allenoate, benzyl 4-methylpenta-2,3-dienoate (**9**), underwent cross-coupling with nitrone **1a**, but the expected product **10** was obtained in only poor yield (22%) and 70% of the starting nitrone **1a** was recovered, along with benzyl 4-methylpent-3-enoate. Steric hindrance in the allenoate may favor its conjugate reduction over cross-coupling with the nitrone.

With γ-N-hydroxyamino esters **4** in hand, an easy-to-perform and high-yielding preparation of β-methylenyl-γ-lactams was developed next. Treatment of **4aa** with zinc in acetic acid, under ultrasound activation at 80 °C, afforded the desired lactam **5a** in nearly quantitative yield (Table 2, entry 1). Following the same procedure, other lactams (**5b**, **5c** and **5g**) were also obtained in good yield (Table 2, entries 2–4).

Scheme 3. Coupling of Nitrone with Substituted Allenoates

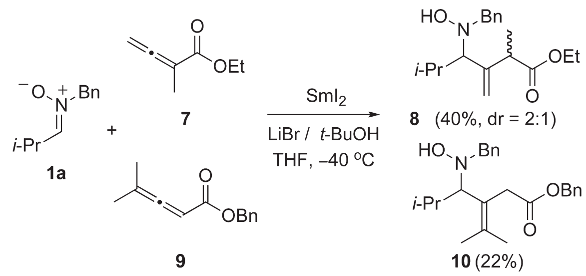
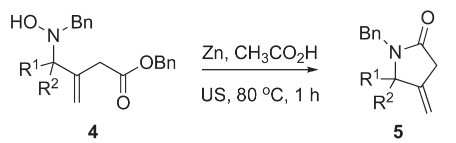


Table 2. Preparation of β-Methylenyl-γ-lactams **5** from N-Hydroxyamino Esters **4**



entry	substrate	R^1	R^2	product (% yield)
1	**4aa**	*i*-Pr	H	**5a** (99)
2	**4ba**	Me	H	**5b** (75)
3	**4ca**	Et	H	**5c** (91)
4	**4ga**	*t*-Bu	H	**5g** (88)

Interestingly, *exo*-β,γ-unsaturated lactams **5** were found to be very stable under both neutral and acidic conditions: after several months, no trace of double bond migration could be observed by NMR analysis of these compounds.

An enantioselective version of the SmI_2-mediated synthesis of β-methylenyl-γ-lactams **5** was next examined with chiral, nonracemic N-*tert*-butanesulfinyl imines (*t*-BS-imines)[21] as the substrates for the cross-coupling with allenoates. *t*-BS-Imines have previously been shown to undergo homocoupling[22] and heterocoupling with aldehydes,[23] nitrones,[24] and methyl methacrylate[3] in the presence of SmI_2. First, the conditions found optimal with nitrone **1a** (Conditions A) were used for the coupling of the R_S-sulfinyl imine **2a** and allenoate **3a** (Table 3, entry 1). The expected product **11a** was obtained in good yield (64%), as a 7:1 mixture of diastereomers, although the reaction was incomplete and 35% of starting sulfinyl imine **2a** was recovered. On increasing the initial concentration of the sulfinyl imine from 18 to 26 mM (Conditions B, Table 3, entry 2), the starting material R_S-**2a** was completely consumed and the yield of **11a** increased to 85%, but the diastereomeric ratio decreased slightly to 5:1. Application of Conditions B to the

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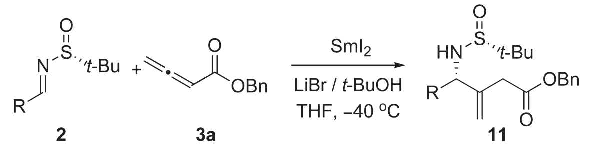
coupling of allenoate **3a** with *t*-BS-imines **2b**–**e** also yielded the expected sulfinamides **11** in high yields and with similar diastereomeric ratios (Table 3, entries 4–7).

Table 3. Scope of the Cross-Coupling between Chiral Sulfinyl Imines **2** and Allenoate **3a**

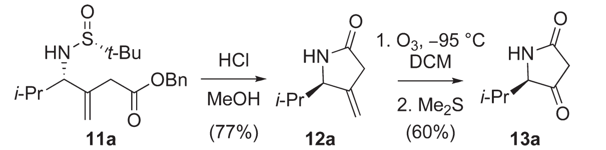


entry	conditions[a]	product (R)	% yield (% recovered imine **2**)	dr[b,c]
1	A	**11a** (*i*-Pr)	64 (35)	7:1
2	B	**11a** (*i*-Pr)	85	5:1
3	A	**11b** (*i*-Bu)	55 (24)	10:1
4	B	**11b** (*i*-Bu)	87	5:1
5	B	**11c** (*c*-Hex)	85	4.5:1
6	B	**11d** (*n*-Pr)	78	5.5:1
7	B	**11e** (Bn)	61	8:1

[a] Conditions A: initial concentration of *t*-BS-imine = 0.18 mM. Conditions B: initial concentration of *t*-BS-imine = 0.26 mM. [b] The dr's were determined by NMR analysis of the crude reaction mixtures. [c] The minor diastereomers are not shown.

The configuration of the newly generated chiral center in compound **11a** (major diastereomer) was assigned from the sign of the optical rotation of the enantioenriched tetramic acid **13a** (Scheme 4). First, the chiral auxiliary in **11a** (5:1 mixture of diastereomers) was removed by treatment with 12 M HCl in methanol, to give the corresponding lactam **12a** in 77% yield. Ozonolysis of **12a** yielded the known enantioenriched tetramic acid **13a** in 60% yield, which was recrystallized to give enantiopure tetramic acid **13a** {$[\alpha]^{20}_{D}$ −42.3 (*c* 0.32, EtOH); lit.[25] −46.4 (*c* 1.00, EtOH)}. Thus, the configuration of the major diastereomer of **11a** was determined to be R_S,*S*.

Scheme 4. Application to the Synthesis of Tetramic Acid **13a**



In conclusion, we have developed a new and efficient approach to β-methylenyl γ-amino esters and γ-lactams through the SmI_2-mediated coupling of allenoates with nitrones and chiral sulfinyl imines. Fine tuning of conditions and use of adequate additives were necessary to ensure selective reduction of the imine derivatives (by electron transfer from SmI_2) rather than the competitive allenoate reduction. The β-methylenyl γ-amino acid derivatives prepared by this methodology can be easily converted to tetramic acids, which are important building blocks for the total synthesis of many natural products, such as sintokamide A,[26] malyngamide X,[27] and gallinamide A.[28]

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Supporting Information Available. Characterization data, full experimental procedures, and copies of ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.