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N-VINYL AND *N*-UNSUBSTITUTED β–LACTAMS FROM 1-SUBSTITUTED 2-AZA-1,3-BUTADIENES

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Abstract: The reaction of acid chlorides and *N*-vinyl imines results in the stereoselective formation of cis *N*-vinyl β-lactams. The *N*-vinyl protecting group can be removed either oxidatively or hydrolytically to yield *N*-unsubstituted β-lactams.

Some of the most versatile methods for the one-step formation of the β-lactam ring system are the enolate-imine condensation[3] and the ketene-imine reaction.[4] Both methods require the use of imines possessing *N*-substituents that are compatible with the respective reaction conditions and which are also easily removable after β-lactam formation.

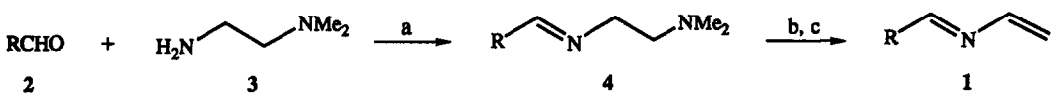
Recently, we have introduced *N*-vinyl imines (2-aza-1,3-dienes) as novel precursors for the synthesis of *N*-(1-propenyl) and *N*-unsubstituted β-lactams[5] via the ketene-imine reaction. Related studies have been reported by Paloma.[6]

N-Vinyl β-lactams were known previously, however, the vinyl group was typically introduced after β-lactam formation and the deprotection to form *N*-unsubstituted β-lactams usually required several steps for completion.[7] The use of 2-aza-1,3-dienes in the ketene-imine reaction represents thus a convergent approach toward the desired *N*-vinyl β-lactams. Requiring only one step for the formation of the β-lactams and one step for the deprotection of the *N*-vinyl β-lactams to form the *N*-unsubstituted β-lactams, the method is straightforward and can be accomplished in good yields. *N*-Unprotected β-lactams are important intermediates in the formation of bicyclic and monocyclic β-lactam antibiotics.[8]

We now wish to report on novel *N*-ethenyl β-lactams synthesized from 1-substituted 2-aza-1,3-butadienes **1** via the acid chloride-imine reaction. We are further detailing the novel observation that the β-lactam *N*-vinyl group can be removed hydrolytically.

The novel 1-substituted 2-aza-1,3-butadienes **1** could be synthesized[5,9] in good yields utilizing a procedure described by Böhme.[10] Reaction of the aldehydes **2** with *N*,*N*-dimethylethylendiamine **3** gave the Schiff bases **4**, which could be purified by vacuum distillation or could also be used crude in the next step of the reaction. In a one flask procedure, the imines **4** were first alkylated with iodomethane in *N*,*N*-dimethylformamide to give the intermediate ammonium iodides. The crude ammonium salts underwent Hoffmann elimination in the presence of sodium hydride to give the desired 2-aza-1,3-butadienes **1** in satisfactory yields (**Table I**).

Table I. Formation of 1-substituted 2-aza-1,3-dienes



(a) Ether, $MgSO_4$, 25°C, 1 h; (b) MeI (2 equiv), DMF, 25°C, 30 min; (c) NaH (3.5 equiv), 0°C, 12 h.

Entry	R	4	Yield (%)	1
1	Ph	83		84[a]
2	PhCH=CH	79		93[b,c]
3	PhCH=CMe	80		63[a]
4	PhC≡C	79		69[b]

[a]Distilled yields. [b]Crude yields. [c]Acetonitrile as the solvent for the conversion of 4 to 1.

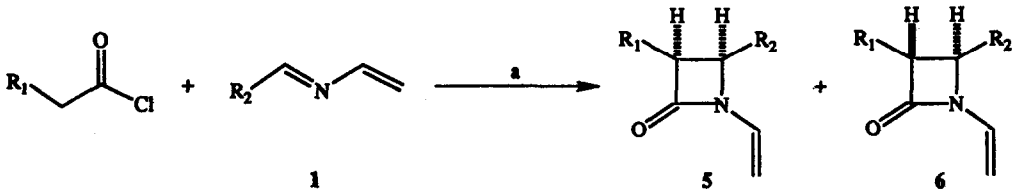
The newly synthesized 2-aza-1,3-butadienes **1** were then subjected to the ketene-imine reaction conditions to generate *N*-vinyl β-lactams **5** and **6** with high cis stereoselectivity[11] and in good yields (**Table II**).

As previously reported,[5-7] the *N*-vinyl group can be removed oxidatively, for example, by treatment with potassium permanganate in an acetone/water solution. Oxidative cleavage of the β-lactam *N*-vinyl group of **5a** under these reaction conditions resulted in the formation of the *N*-unprotected β-lactam **7** in 90% yield. It should be pointed out that the short reaction time (10 min) is crucial in this reaction. A longer reaction time results in a decreased yield of the *N*-unprotected β-lactam **7** (**Scheme 1**).

We also explored the possibility of an acid catalyzed hydrolysis of the *N*-vinyl β-lactam moiety (enamide functionality). Refluxing *N*-vinyl β-lactam **5a** in THF/1% aq HCl (9:2) for 36 h afforded a 1:1 mixture of the *N*-unprotected β-lactam **7** and the *N*-hydroxyethyl β-lactam **8** (as a mixture of diastereoisomers). Treatment of the mixture consisting of **7** and **8** with aqueous Na_2CO_3 solution produced β-lactam **7** in an overall yield of 62%. The *N*-hydroxyethyl group in **8** is also cleaved upon column chromatography on silica gel.

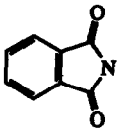
The enamine like behavior of the *N*-vinyl group of the β-lactams allows now for an easy differentiation of the two double bonds, for example, in β-lactam **5c**. Oxidative cleavage with potassium permanganate results, as expected, in a simultaneous oxidation of both double bonds to produce the 4-acetyl-β-lactam **9** in 78% yield. However, hydrolysis keeps the 4-vinyl group intact, and cleaves only the *N*-vinyl group to yield β-lactam **10** in 81% yield (**Scheme 2**).

Table II. Ketene-imine reaction with 1-substituted 2-aza-1,3-butadienes

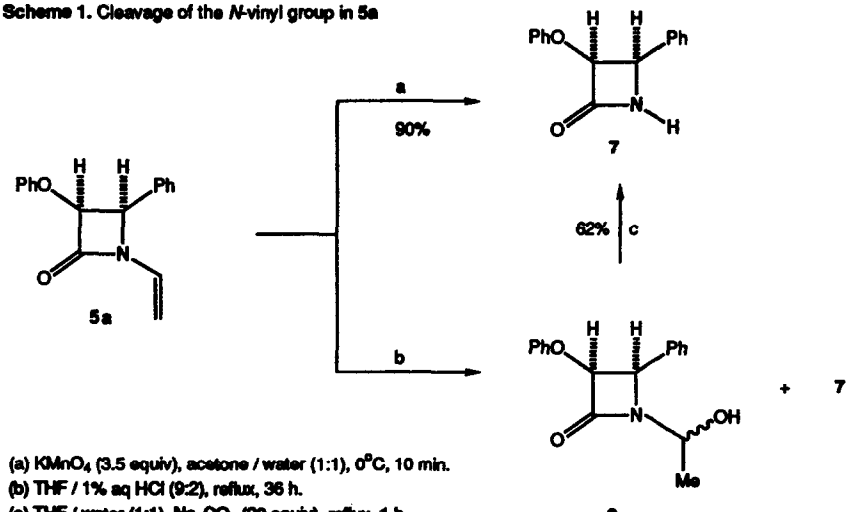


1 5 6

(a) Triethylamine (3 equiv), dichloromethane, acid chloride (3 equiv), 25°C, 12 h.

Entry	R_1	R_2		5 (% yield)	6 (% yield)
1	PhO	Ph	5a	93	3
2	PhO	PhCH=CH	5b	77	-
3	PhO	PhCH=CMe	5c	80	2
4		PhCH=CMe	5d	63	-
5	PhO	Ph–≡	5e	45	14

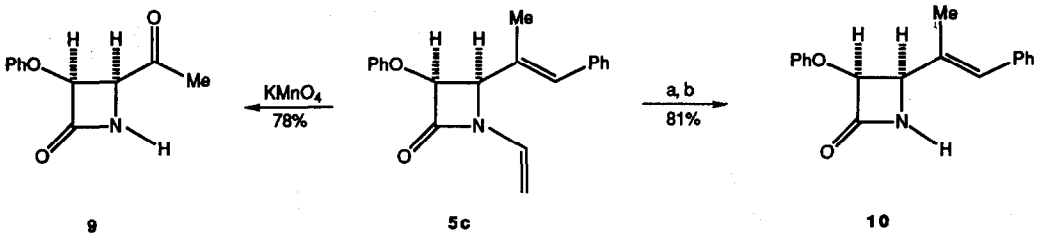
Scheme 1. Cleavage of the *N*-vinyl group in 5a



5a 7 8

(a) $KMnO_4$ (3.5 equiv), acetone / water (1:1), 0°C, 10 min.
(b) THF / 1% aq HCl (9:2), reflux, 36 h.
(c) THF / water (1:1), Na_2CO_3 (20 equiv), reflux, 1 h.

Scheme 2. Selective cleavage of the double bonds in β-lactam 5c



9 5c 10

(a) THF/1 % aq HCl (9:2), reflux, 36 h.
(b) THF/water (1:1), Na_2CO_3 (20 equiv.) reflux, 1 h.

With this letter we have demonstrated the utility of 2-aza-1,3-dienes in β-lactam chemistry and we have also shown that the *N*-vinyl protecting group can be removed either oxidatively or hydrolytically.

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