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Coupling of vinyl aziridines and phenyl isocyanate

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ABSTRACT

Thermal coupling of vinyl aziridines and phenyl isocyanate was evaluated. Although oxazolidinone products were predominant, some reactions afforded a seven-membered ring heterocycle. When Ni/IMes was employed as a catalyst, a wider array of vinyl aziridines underwent coupling reactions. The Ni catalyzed reactions generally afforded vinyl imidazolidinones as major products.

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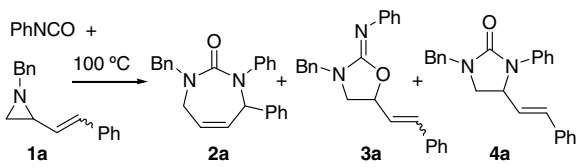
The coupling of an isocyanate and a vinylaziridine is an effective way to access heterocyclic ring systems. Although one example of a thermal coupling has been reported,[1] these reactions are typically catalyzed by Lewis acids such as sodium iodide[2] and nickel iodide.[3] These couplings generally afford vinyl-substituted five-membered imidazolidinone products. Palladium catalysts have also been used to catalyze this coupling reaction and in some cases, these couplings display high enantioselectivity.[4–6] In each of these cycloadditions, the vinyl group acts to enhance the reactivity of the aziridine. For example, in non-metal mediated reactions the vinyl group is an activating group. In Pd catalyzed coupling reactions, the vinyl group enhances binding of the aziridine substrate. However, in all of these cases, incorporation of the vinyl group *in* the heterocycle is not observed.

We present here a study detailing both thermal reactions and nickel catalyzed reactions of phenyl isocyanate and vinyl aziridines. These reactions afford interesting heterocyclic products in addition to the expected vinyl-substituted imidazolidinone.



(1)

Despite the lack of information regarding simple thermal coupling of isocyanates and vinyl aziridines, we found that *N*-benzyl-2-styryl-aziridine (**1a**) reacted readily with 3 equiv of phenyl isocyanate at elevated temperatures (Eq. 1). At 100 °C, the coupling proceeded smoothly and afforded three distinct heterocyclic products, a seven-membered product (**2a**), an oxazolidinone **3a**,[7] and a trace amount of imidazolidinone **4a**[7] (Eq. 1).

A variety of vinyl azirdines were evaluated in the thermal coupling reaction (Table 1, Eq. 2).[8] Electronic factors did not have much of an effect on the reaction as both para methoxy and para CF_3 substituted substrates afforded relatively equal ratios of heterocyclic products **2** and **3** (entries 2 and 3). The reaction with **1b** also afforded a vinyl-substituted imidazolidinone (**4b**) in trace amounts. Additional substitution on the olefin led to the selective formation of the oxazolidine product **3** (entries 5 and 6). In entry 6 where the substrate lacks an activating phenyl group (**1f**), the reaction was quite sluggish. Only 38% of the **3f** was isolated. When the *N*-benzyl group was replaced by an *N*-cyclohexyl group, the seven-membered ring (**2g**) was slightly favored over the oxazolidine ring (**3g**). Other substitution patterns lead to no heterocyclic products. Terminal vinyl aziridines possessing no activating group (i.e., R = Bn, R_1, R_2 = H, H, **1h** and R = Cy, R_1, R_2 = H, H, **1i**) did not react. In addition, when N was substituted with a bulky *tert*-butyl group (i.e., R = *t*-Bu, R_1, R_2 = H, Ph, **1j**) or when the phenyl group was replaced with an ester group (i.e., R = Bn, R_1, R_2 = H, CO_2Et, **1k**), no reaction took place. *N*-Phenyl-vinylaziridines underwent a Ni catalyzed [3,3] sigmatropic rearrangement.[9]

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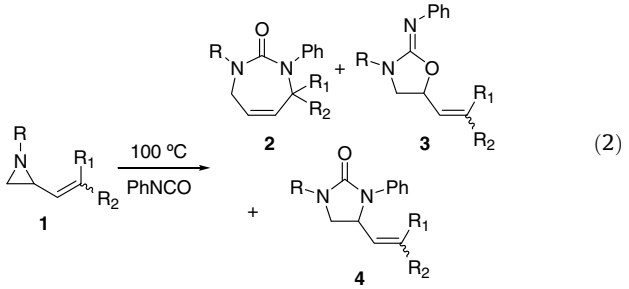
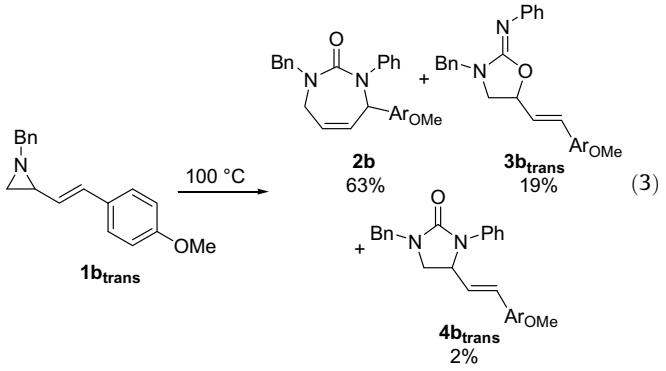
Table 1
Thermal coupling of PhNCO and vinyl aziridines[a]



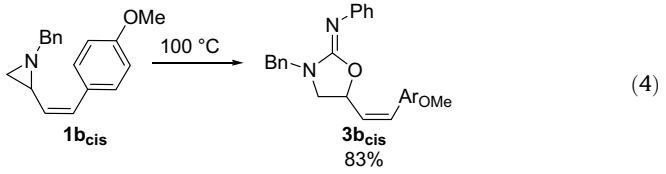
(2)

Entry	Vinyl aziridine			(% Yield)		
	1	R	R_1, R_2	**2**	**3**	**4**
1	**1a**[b]	Bn	H, Ph	**2a** (41)[c]	**3a** (39)[c]	**4a** (9)[c]
2	**1b**[b]	Bn	H, 4-C_6H_4–OMe	**2b** (42)[c]	**3b** (36)[c]	**4b** (3)[c]
3	**1c**[b]	Bn	H, 4-C_6H_4–CF_3	**2c** (25)[d]	**3c** (28)[d]	
4	**1d**[b]	Bn	H, –C_2H_3	**2d** (42)[d]	**3d** (40)[d]	
5	**1e**[b]	Bn	Me, Ph		**3e** (74)[c]	
6	**1f**	Bn	Me, Me		**3f** (38)[c]	
7	**1g**[b]	Cy	H, Ph	**2g** (36)[c]	**3g** (20)[c]	

[a] Reaction conditions: 0.1 M vinyl aziridine, 0.3 M isocyanate, toluene, 100 °C.
[b] Mixture of cis and trans.
[c] Isolated yields.
[d] GC or NMR yields determined relative to an internal standard.



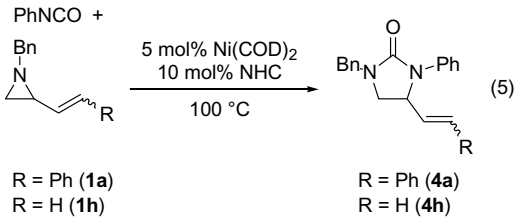
(3)



(4)

In an effort to differentiate the reactivity of *cis* and *trans* vinyl aziridines, the cis and trans isomers of **1b** were evaluated individually in the thermal rearrangement reaction (Eqs. 3 and 4). Interestingly, oxazolidinone products were observed in both reactions. However, the seven-membered ring product (**2b**) was only observed in the reaction of the *trans* vinyl aziridine.

We have recently found that the combination of $Ni(COD)_2$ and NHC ligands catalyze the reaction of vinyl aziridines and alkynes.[10] We surmised that this catalyst combination may facilitate the coupling of a wider range of vinyl aziridines and isocyanates and in a selective manner. As such, a series of NHCs were evaluated as potential ligands (Fig. 1) for the Ni(0) catalyzed cycloaddition of isocyanates and vinylaziridines. Phenyl isocyanate (0.3 M)[11] and *N*-benzyl-2-styryl-aziridine (**1a**, 0.1 M) were again chosen as model substrates in a reaction catalyzed by 5 mol % $Ni(COD)_2$ and 10 mol % NHC in toluene at 100 °C (Eq. 5). Again, three heterocyclic products were generally observed. However, unlike the thermal



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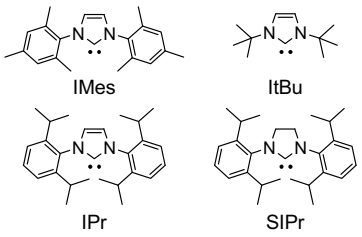


Figure 1. NHC ligands.

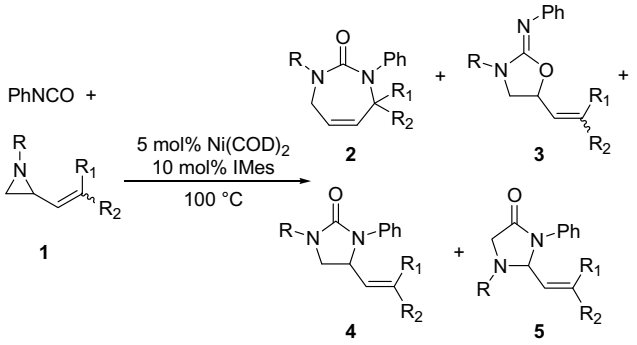
reactions described above, **4a** was formed as the major product in almost all Ni/NHC catalyzed reactions. The use of IPr or SIPr afforded **2a**, **3a**, and **4a** in relatively equal amounts. Vinyl imidazolidinone **4a** was the major product when either IMes or I*t*Bu was employed; however, yields and ratios of **4a** were higher when IMes was used as the ligand.

When an unactivated vinyl aziridine (**1h**) was used as a model substrate in lieu of **1a**, only the formation of imidazolidinone **4h** was observed (Eq. 5). The products obtained from thermal reactions, such as the seven-membered product (**2h**) and the oxazolidinone (**3h**), were not observed in appreciable amounts.[12] Although the combination of Ni/IMes did catalyze the coupling of **1h** and PhNCO (43% NMR yield), higher yields of **4h** were formed in the presence of I*t*Bu (83% NMR yield). Similar results were obtained when *N*-cyclohexyl-vinylaziridine (**1i**) was used as a model substrate.

The Ni/IMes catalyzed coupling of vinyl aziridines and phenyl isocyanate proved to be a more general reaction than thermal reactions (Table 2).[13] Activated vinyl aziridines reacted smoothly with PhNCO (entries 1–5). In most cases, imidazolidinone (**4**) was formed preferentially. Only the reaction of **1b** and **1e** gave slightly more seven-membered ring **2b** or oxazolidinone **3e**, respectively (entries 2 and 5). In contrast to the thermal reactions shown in Table 1, unactivated vinyl aziridines were also converted to heterocyclic products. For example, the thermal reaction of **1f** was sluggish (Table 1, 38% **3f**), whereas it afforded heterocyclic products (**3f** and **4f**) in an overall 64–67% yield in the Ni/NHC catalyzed reaction (entries 6a and b). In addition, terminal vinyl aziridines gave imidazolidinone products exclusively and in generally good yields (40% and 60%, entries 8a and 9a, respectively); higher yields were observed with the Ni/I*t*Bu catalysts (70% and 92%, entries 8b and 9b, respectively). Other vinyl aziridines such as **1j** and **1k**, which were unreactive under thermal conditions, did undergo Ni/IMes catalyzed coupling. Interestingly, the steric hinderance of **1j** resulted in the formation of small amounts of a unique heterocycle (**5j**). It appears that with this substrate, C–C bond cleavage competes with the more favorable C–N bond cleavage of the aziridine (entry 10). *N*-Phenyl-substituted vinyl aziridines afforded low amounts of imidazolidinone products in addition to aza-cope products (entries 12 and 13).

The amount of catalyst had a profound effect on the ratio of heterocyclic products in these reactions. Specifically, we found that increasing the catalyst loading resulted in the increase of the generation of the imidazolidinone derivative **4a**. On the other hand, reducing the catalyst promoted the formation of the seven-

Table 2
Nickel catalyzed coupling of PhNCO and vinyl aziridines



(6)

Entry	Vinyl aziridine			(% Yield)			
	1	R	R_1, R_2	**2**	**3**	**4**	**5**
1	**1a**[c]	Bn	H, Ph	**2a** (5)[a,d]		**4a** (55)[a,d]	
2	**1b**[c]	Bn	H, 4-C_6H_4–OMe	**2b** (30)[a,d]	**3b** (11) [a,d]	**4b** (24)[a,d]	
3	**1c**[c]	Bn	H, 4-C_6H_4–CF_3	**2c** (6)[e]		**4c** (69)[e]	
4	**1d**[c]	Bn	H, –C_2H_3	**2d** (13)[e]	**3d** (13)[e]	**4d** (41)[e]	
5	**1e**[c]	Bn	Me, Ph		**3e** (60)[a,d]	**4e** (18)[a,d]	
6a	**1f**	Bn	Me, Me		**3f** (27)[a,d]	**4f** (37)[a,d]	
6b					**3f** (30)[a]	**4f** (37)[b,d]	
7	**1g**[c]	Cy	H, Ph			**4g** (81)[a,d]	
8a	**1h**	Bn	H, H			**4h** (40)[a,d]	
8b						**4h** (70)[b,d]	
9a	**1i**	Cy	H, H			**4i** (60)[a,d]	
9b						**4i** (92)[b,d]	
10	**1j**[c]	*t*-Bu	H, Ph	**2j** (7)[a,d]		**4j** (16)[a,d]	**5j** (15)[a,d]
11	**1k**[c]	Bn	H, CO_2Et			**4k** (65)[a,d]	
12	**1l**	Ph	H, H			**4l** (13)[a,d]	
13	**1m**[c]	Ph	H, Ph			**4m** (35)[a,d]	

[a] Reaction conditions: 5 mol % Ni(COD)$_2$, 10 mol % IMes, 0.1 M vinyl aziridine, 0.3 M isocyanate, toluene, 100 °C.
[b] Reaction conditions: 5 mol % Ni(COD)$_2$, 10 mol % I*t*Bu, 0.1 M vinyl aziridine, 0.3 M isocyanate, toluene, 100 °C.
[c] Mixture of cis and trans.
[d] Isolated yields.
[e] GC yields determined relative to an internal standard.

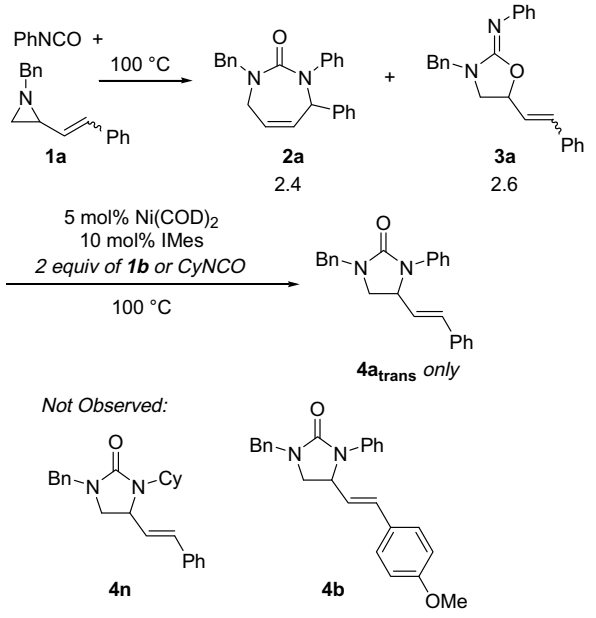
membered ring product **2a** (Table 3). It may be possible that the Ni/IMes catalyst serves to enhance the formation of the more thermodynamically favored imidazolidinone products (**4**). A similar phenomenon has been observed in nickel iodide promoted couplings.[3]

Given the results in Table 3, it was unclear whether **4a** was formed from a rearrangement of **2a** and **3a** or whether it was formed directly from **1a** and PhNCO. In addition, it may be possible for **2a** and **3a** to revert back to PhNCO and vinyl aziridine before ultimately affording **4a**. To address these possibilities, **1a** and PhNCO were heated to 100 °C until a mixture of **2a** and **3a** was obtained. Two equivalents of **1b** and catalytic amounts of Ni(COD)$_2$ and IMes were then added to the solution and the reaction was further heated to 100 °C. Interestingly, **4a$_{trans}$** was the only observed product (Scheme 1). No products (i.e., **4b**) arising from the reaction of **1b** and PhNCO were observed. Similarly, no products (i.e., **4n**) arising from the reaction of **1a** and CyNCO were observed when CyNCO was added in lieu of **1b** (Scheme 1). Thus, formation of heterocyclic products (**2**–**4**) appears to be irreversible in both thermal and nickel catalyzed reactions.

Table 3
Ni/IMes catalyzed coupling of PhNCO and **1a**[a]

Entry	% Ni(COD)$_2$	% IMes	Ratio of products[b]		
			2a	**3a**	**4a**
1	10	20	1	0	24
2	5	10	1	0	11
3	1	2	1	0	1.5
4	0.1	0.2	1.6	0	1

[a] Reaction conditions: 0.1 M **1a**, 0.3 M PhNCO, toluene.
[b] Determined by GC using naphthalene as an internal standard.



Scheme 1. NMR analysis of Ni catalyzed rearrangement of thermal coupling products.

In summary, thermal and Ni/IMes-catalyzed reactions of phenyl isocyanate and various vinyl aziridines were evaluated. Thermal reactions generally afford oxazolidinone products. In some cases, a seven-membered heterocycle is also formed. Ni catalyzed reactions generally afforded the more thermodynamically favored imidazolidinone product.

Acknowledgments

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8. General procedure for the thermal reactions: A toluene solution of PhNCO (75.9 mg, 0.637 mmol, 0.3 M) and vinylaziridine **1a** (50 mg, 0.212 mmol, 0.1 M) was heated to 100 °C for 8 h. The reaction mixture was cooled and the solvent was removed in vacuo. The residue was purified by flash chromatography (2:3 diethyl ether: pentane) to afford imidazolidinone **4a** (6.8 mg, 9%) and the seven-membered ring **2a** (30.9 mg, 41%), and oxazolidinone **3a** (29.4 mg, 39%). *1-Benzyl-3,4-diphenyl-1,3,4,7-tetrahydro-[1,3]diazepin-2-one* (**2a**): Light yellow oil. IR (dissolved in methylene chloride) ν: 1656, 1464, 1240 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.42–7.13 (m, 13H), 6.96 (q, 2H), 6.11 (m, 1H), 5.86 (m, 1H), 5.40 (d, 5.7 Hz, 1H), 4.632 (d, 15 Hz, 1H), 4.18–4.08 (m, 2H), 3.46 (dd, 1H). ^{13}C NMR (300 MHz, $CDCl_3$, ppm) δ: 47.5, 53.6, 65.0, 125.3, 125.3, 125.9, 127.3, 127.4, 127.6, 128.5, 128.7, 128.9, 129.1, 130.1, 138.0, 141.9, 146.4, 163.9. EIMS *m*/*z*: 354 (M^+), 220, 206, 144, 115, 91. HRMS(ESI/APCI) for $C_{24}H_{23}N_2O$

[M+H]$^+$: calcd. 355.1810, found 355.1807. (*3-Benzyl-5-styryl-oxazolidin-2-ylidene)-phenyl-amine* (**3a$_{trans}$**): Light yellow oil. IR (dissolved in methylene chloride) ν: 1672, 1591 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.42–7.17 (m, 14H), 6.97 (t, 1H), 6.65 (d, 15.9 Hz, 1H), 6.18 (q, 1H), 4.68 (d, 15 Hz, 1H), 4.55 (d, 15 Hz, 1H), 3.56 (t, 1H), 3.19 (dd, 1H). ^{13}C NMR (300 MHz, $CDCl_3$, ppm) δ: 49.5, 50.9, 77.4, 122.3, 123.8, 125.4, 127.0, 127.9, 128.6, 128.7, 128.8, 128.9, 134.8, 135.8, 137.0, 147.8, 152.8. EIMS *m*/*z*: 354 (M$^+$), 250, 206, 91, 28. HRMS(ESI/APCI) for $C_{24}H_{23}N_2O$ [M+H]$^+$: calcd. 355.1810, found 355.1802. (*3-Benzyl-5-styryl-oxazolidin-2-ylidene)-phenyl-amine* (**3a$_{cis}$**) Light yellow oil. IR (dissolved in methylene chloride) ν: 1675, 1591, 1493 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.40–7.14 (m, 13H), 6.96 (t, 1H), 6.75 (d, 11.4 Hz, 1H), 5.76 (dd, 1H), 5.31 (q, 1H), 4.66 (d, 15 Hz, 1H), 4.54 (d, 15 Hz, 1H), 3.54 (t, 1H), 3.17 (t, 1H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ: 49.5, 51.3, 72.7, 122.1, 123.8, 127.9, 128.2, 128.6, 128.7, 128.9, 135.5, 135.7, 137.0, 147.8, 152.8. EIMS *m*/*z*: 354 (M$^+$), 250, 206, 91, 28. HRMS(ESI/APCI) for $C_{24}H_{23}N_2O$ [M+H]$^+$: calcd. 355.1810, found 355.1811.

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11. NHC catalyze the cyclotrimerization of isocyanates. (See Duong, H. A.; Cross, M. J.; Louie, J. *Org. Lett.* **2004**, *6*, 4679.) Thus, excess isocyanate provided optimal reaction conditions.
12. No reaction occurred when couplings were run in the presence of $Ni(COD)_2$ and NHC alone.
13. General procedure for $Ni(COD)_2$/NHC catalyzed reaction: In glovebox, a scintillation vial equipped with a magnetic stir bar was charged with PhNCO (75.9 mg, 0.637 mmol, 0.3 M) and vinylaziridine **1a** (50 mg, 0.212 mmol, 0.1 M) in toluene. A solution of $Ni(COD)_2$ (2.9 mg, 0.0106 mmol, 0.005 M) and IMes (6.5 mg, 0.0212 mmol, 0.01 M) in toluene was added. The reaction was stirred at 100 °C for 6 h. The reaction was cooled and the solvent was removed in vacuo. The residue was purified by flash chromatography (2:3 diethyl ether/pentane) to afford imidazolidinone **4a** (41.4 mg, 55%) and the seven-membered ring **2a** (3.77 mg, 5%). *1-Benzyl-3-phenyl-4-styryl-imidazolidin-2-one* (**4a$_{trans}$**): Light yellow oil. IR (dissolved in methylene chloride) ν: 1701, 1499, 1423 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.56–7.02 (m, 16H), 6.59 (d, 15.9 Hz, 1H), 6.13 (q, 1H), 4.80 (q, 1H), 4.58 (d, 15 Hz, 1H), 4.44 (d, 15 Hz, 1H), 3.60 (t, 1H), 3.13 (dd, 1H). ^{13}C NMR (300 MHz, $CDCl_3$, ppm) δ: 48.3, 48.8, 56.5, 120.8, 123.5, 126.8, 127.8, 128.0, 128.4, 128.5, 128.8, 128.9, 133.5, 136.1, 137.0, 139.5, 158.2. EIMS *m*/*z*: 354 (M$^+$), 263, 250, 223, 206, 91. HRMS(ESI/APCI) for $C_{24}H_{23}N_2O$ [M+H]$^+$: calcd. 355.1810, found 355.1806.