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Nickel-catalyzed reactions of vinyl aziridines and aziridinylen-ynes

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Abstract

Ni/NHC was found to catalyze the rearrangement of vinyl aziridines and aziridinylen-ynes under mild conditions.

Keywords

nickel catalyst; N; heterocyclic carbene; vinyl aziridine; aziridinylen; ynes; imines; heterocycles

A primary interest of our group is the development of efficient cycloadditions that afford heterocycles and carbocycles. We have found that Ni/NHC complexes effectively catalyze the cycloaddition of diynes with CO₂¹, isocyanates,² carbonyls,³ and nitriles.⁴ These reactions afford pyrones, pyridones, pyrimidinones, pyrans, and pyridines in high yields. In addition, the same Ni/NHC system also mediates the rearrangement of vinyl cyclopropanes⁵ and cyclopropylen-ynes.⁶ As part of our continuing effort in this field⁷ we present our investigations involving the Ni catalyzed reactions of vinyl aziridines^{8,9} and aziridinylen-ynes.

(1)

The Ni-catalyzed rearrangement of 1-trityl-2-vinylaziridine (**1a**)¹⁰ was investigated, and a variety of tertiary phosphines and N-heterocyclic carbene ligands (NHCs)¹¹ were explored as potential ligands (equation 1, Table 1). In most cases, no reaction was observed (entries 2–7). However, when IPr was employed, vinylaziridine **1a** was smoothly converted to an α,β -

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unsaturated imine **2a**¹² (entry 1).¹³ No rearrangement was observed in the absence of ligand (entry 8).

(2)

It is known that the type of protecting group can have a large influence in the product that is obtained.^{8,14,15,16} As such, a variety of vinylaziridines containing different protecting groups were investigated using Ni(COD)₂/NHC as catalyst (equation 2, Table 2).¹⁷ Most vinylaziridines underwent rearrangements at room temperature except 1-tosyl vinylaziridine (**1f**)¹⁸ which destroyed the catalyst (entry 7). The Ni/NHC catalyzed rearrangements of vinylaziridines were highly substrate-dependent. 1-Benzoyl vinylaziridine (**1b**),¹⁹ 1-Boc vinylaziridine (**1c**)²⁰ and 1-methoxycarbonyl vinylaziridine (**1d**)²¹ isomerized to the corresponding 5-vinyl-2-oxazoline (entries 2–4).^{22, 23} Interestingly, the Ni/IPr catalyzed rearrangement of 1-benzhydryl vinylaziridine (**1e**)²⁴ did not afford an α , β -unsaturated imine. Instead, a 1,3-butadienylamine (**2e**) was obtained (entry 5). However, when IPr was replaced with its saturated analog, SIPr, **1e** was converted to the expected α , β -unsaturated imine **2e'** (entry 6).

The rearrangement of vinylaziridines to imines or 1,3-butadienylamines can be rationalized by the formation of a key π -allyl/Ni complex (Scheme 1). Due to the difficulty of reductive elimination of C(sp³)-N bond,²⁵ this π -allyl/Ni complex undergoes β -hydride elimination followed by reductive elimination. 1,3-Butadienylamine or imine arises from metallazetidine intermediate (**3e'**) or metallapiperidine intermediate (**3e**) respectively.

In an effort to block competing β -hydride elimination pathways, the cycloaddition of a vinyl aziridine possessing a tethered alkyne was evaluated. 1-Trityl-2-(3-(2-butyloxy)-1-propenyl)-aziridine (**4a**)²⁶ was subjected to standard cycloaddition conditions in the presence of a variety of ligands (Table 3). No rearrangement was observed in the absence of ligand or when tertiary phosphines were used as ligands (entries 1–3). However, aziridinyl-ene **4a** did react when NHCs were employed (entries 4–7). Interestingly, the rearrangement of aziridinyl-ene **4a** afforded three different products whose ratios were dependent on which NHC ligand was employed. NHCs possessing an aromatic side chain (IPr, SIPr and IMes) afforded two different azepines (**5a** and **6a**). IMes favored the formation of azepine **6a** (entry 4) whereas SIPr favored the formation of azepine **5a** (entry 6).²⁷ IPr showed no selectivity between these two azepines even at lower catalyst loading and less reaction time. In contrast, the Ni/ItBu catalyzed rearrangement of aziridinyl-ene **4a** gave a conjugated unsaturated imine (**7a**) selectively, which is consistent with the Ni/ItBu catalyzed rearrangement of cyclopropen-ene.⁶

(3)

Other aziridinylen-yne possessing a bulky protecting group (i.e., *t*-butyl (**4b**)²⁸ and benzhydryl (**4c**),²⁹ Figure 1) also underwent Ni-catalyzed rearrangement reactions. Conjugated imine products (**7b-c**) were again observed exclusively when *It*Bu was employed. Similarly, a mixture of bicyclic azepines (i.e., **5b-c** and **6b-c**) were observed when *N*-aryl NHCs (i.e., IMes, IPr, SIPr) were employed. Interestingly, azepines **5** and **6** appear to arise from C-C cleavage, rather than C-N cleavage, of the aziridine ring. It is possible that the steric hindrance of *N*-protecting groups prevent the nitrogen atom from coordinating to nickel center and disfavor C-N bond cleavage.

In summary, the combination of $\text{Ni}(\text{COD})_2$ and a bulky NHC ligand serves as a catalyst for the rearrangement of vinyl aziridines and aziridinylen-yne. Vinyl aziridines were typically converted to straight chain products. Aziridinylen-yne afforded a mixture of heterocyclic products. Mechanistic investigations are ongoing.

Acknowledgments

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10. 1a: ¹H NMR (300 MHz, CDCl₃, ppm): δ 7.48 (d, 7.2 Hz, 6H), 7.20–7.30 (m, 9H), 5.83 (ddd, 7.8 Hz, 10.2 Hz, 17.4 Hz, 1H), 5.25 (d, 17.4 Hz, 1H), 5.16 (d, 10.2 Hz, 1H), 1.81 (d, 3.0 Hz, 1H), 1.69–1.73 (m, 1H), 1.35 (d, 6.0 Hz, 1H); ¹³C { ¹H } NMR (75 MHz, CDCl₃, ppm): δ 144.6, 139.4, 129.8, 127.6, 126.8, 116.5, 74.5, 35.0, 29.2.
11. IPr = 1,3-bis(2,6-diisopropylphenyl)-imidazol-2-ylidene; SIPr = 1,3-bis(2,5-diisopropylphenyl)-4,5-dihydroimidazolin-2-ylidene; IMes = 1,3-bis(2,4,6-trimethylphenyl)-imidazol-2-ylidene; IrBu = 1,3-di-*tert*-butylimidazol-2-ylidene.
12. 2a: ¹H NMR (300 MHz, CDCl₃, ppm): δ 7.61 (d, 1H), 7.49 (d, 6H), 7.09–7.20 (m, 9H), 6.60 (dd, 1H), 5.53 (dq, 1H), 1.45 (d, 3H).
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17. 2b: ¹H NMR (300 MHz, CDCl₃, ppm): δ 8.09 (d, 2H), 7.04–7.10 (m, 3H), 5.26 (ddd, 1H), 5.10 (dd, 1H), 4.90 (dd, 1H), 4.89 (dt, 1H), 3.83 (dd, 1H), 3.59 (dd, 1H); 2c: ¹H NMR (300 MHz, CDCl₃, ppm): δ 5.60 (ddd, 1H), 5.03 (dd, 1H), 4.83 (dd, 1H), 4.50 (dt, 1H), 3.72 (dd, 1H), 3.40 (dd, 1H), 1.50 (s, 9H); 2e: ¹H NMR (300 MHz, CDCl₃, ppm): δ 7.42–7.54 (m, 4H), 7.10–7.20 (m, 6H), 6.32 (dt, 1H), 6.08 (dd, 1H), 5.24 (dd, 1H), 5.18 (d, 1H), 4.92 (dd, 1H), 4.78 (dd, 1H), 3.25 (br, 1H) ppm; 2e' ¹H NMR (300 MHz, CDCl₃, ppm): δ 7.79 (d, 1H), 7.49 (d, 4H), 7.09–7.20 (m, 6H), 6.43 (dd, 1H), 5.76 (dq, 1H), 5.32 (s, 1H), 1.45 (d, 3H).
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20. 1c: ¹H NMR (300 MHz, C₆D₆, ppm): δ 5.35 (ddd, 17.1 Hz, 9.9 Hz, 7.2 Hz, 1H), 5.20 (dd, 17.1 Hz, 1.8 Hz, 1H), 4.95 (dd, 9.9 Hz, 1.8 Hz, 1H), 2.62–2.68 (m, 1H), 2.10 (d, 6.3 Hz, 1H), 1.80 (d, 3.6 Hz, 1H), 1.35 (s, 9H); ¹³C { ¹H } NMR (75 MHz, C₆D₆, ppm): δ 161.8, 135.9, 117.8, 80.4, 39.2, 32.6, 27.9.
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24. 1e: ¹H NMR (300 MHz, CDCl₃, ppm): δ 7.15–7.83 (m, 11H), 5.68 (m, 1H), 5.26 (dd, 17.1 Hz, 1.2 Hz, 1H), 5.11 (dd, 10.2 Hz, 1.2 Hz, 1H), 3.59 (s, 1H), 2.11 (m, 1H), 1.88 (d, 3.3 Hz, 1H), 1.73 (d, 6.6 Hz, 1H).
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26. 1-Trityl-2-(3-(2-butynyloxy)-1-propenyl)-aziridine (4a) ¹H NMR (300 MHz, CDCl₃, ppm): δ 7.28 (d, 7.2 Hz, 6H), 7.20–7.29 (m, 9H), 5.75–5.77 (m, 2H), 4.11–4.13 (m, 2H), 4.06–4.08 (m, 2H), 1.88 (t, 1.8 Hz, 3H), 1.80–1.81 (m, 1H), 1.75–1.78 (m, 1H), 1.24 (d, 6.3 Hz, 1H); ¹³C { ¹H } NMR (75

MHz, CDCl₃, ppm): δ 144.6, 135.6, 129.7, 128.0, 127.6, 126.9, 82.6, 74.5, 69.7, 58.4, 57.4, 33.9, 29.3, 3.8.

27. Azepine 5a could be isolated in 66% yield. Unfortunately, azepine 6a decomposed upon all purification attempts. General procedure: In a glove box, 2-(3-(2-butynyloxy)-1-propenyl)-1-triphenylmethyl-aziridine (4a, 50 mg, 0.13 mmol) was added to an oven dried scintillation vial equipped with a magnetic stir bar and dissolved in toluene (0.5 mL). To the stirring solution, a solution of Ni(COD)₂ (2 mg, 0.007 mmol) and SIPr (5 mg, 0.013 mmol) was added. The reaction mixture was stirred at room temperature overnight (or until complete consumption of starting material was observed as judged by GC or TLC). The mixture was concentrated in vacuo and purified by silica gel column chromatography (10% Et₂O/pentanes) to afford 3-(1,3-butadienyl)-4-ethylidenetetrahydrofuran (5a, 33 mg, 66%) as a colorless oil. ¹H NMR (300 MHz, C₆D₆, ppm): δ 7.2 Hz, 6H), 6.97–7.14 (m, 9H), 6.47 (d, 9.3 Hz, 1H), 4.70–4.90 (m, 4H), 4.59 (d, 9.3 Hz, 1H), 3.34 (dd, 1.5 Hz, 12.9 Hz, 1H), 2.76–2.83 (m, 1H), 2.41 (dd, 7.8 Hz, 12.9 Hz, 1H), 0.60 (d, 7.2 Hz, 3H); ¹³C {¹H} NMR (75 MHz, C₆D₆, ppm): δ 144.8, 141.3, 133.6, 130.0, 129.0, 127.2, 94.9, 80.1, 79.4, 56.0, 36.0, 17.5.
28. 1-*tert*-Butyl-2-(3-(2-butynyloxy)-1-propenyl)-aziridine (4b) ¹H NMR (300 MHz, CDCl₃, ppm): δ 5.81 (dt, 6.6 Hz, 15.6 Hz, 1H), 5.48 (dd, 7.8 Hz, 15.6 Hz, 1H), 4.05–4.07 (m, 2H), 3.99 (d, 6.6 Hz, 2H), 2.11–2.15 (m, 1H), 1.8 (t, 1.8 Hz, 3H), 1.69 (d, 6.6 Hz, 1H), 1.50 (d, 3.0 Hz, 1H), 0.97 (s, 9H); ¹³C {¹H} NMR (75 MHz, CDCl₃, ppm): δ 136.2, 127.2, 82.6, 75.3, 69.9, 57.7, 53.3, 32.8, 28.4, 26.7, 3.8.
29. 1-Benzhydryl-2-(3-(2-butynyloxy)-1-propenyl)-aziridine (4c) ¹H NMR (300 MHz, C₆D₆, ppm): δ 7.43–7.56 (m, 4H), 7.04–7.16 (m, 6H), 5.75 (dt, 5.4 Hz, 15.3 Hz, 1H), 5.62 (dd, 7.2 Hz, 15.3 Hz, 1H), 4.02 (q, 2.1 Hz, 2H), 3.94 (d, 5.4 Hz, 2H), 3.33 (s, 1H), 1.80–1.84 (m, 1H), 1.62 (d, 3.3 Hz, 1H), 1.47 (t, 2.1 Hz, 3H), 1.33 (d, 6.6 Hz, 1H); ¹³C {¹H} NMR (75 MHz, C₆D₆, ppm): δ 144.2, 144.0, 133.5, 127.2, 127.0, 82.0, 78.4, 76.1, 69.3, 57.5, 40.7, 35.8, 3.2.

Figure 1.
Aziridinyl-ynes

Scheme 1.
Proposed mechanism of rearrangements of vinylaziridines.

Table 1Ni-catalyzed rearrangements of **1a**^a

Entry	ligand	% Conv. of 1a ^b
1	IPr	100
2	SIPr	trace
3	IMes	0
4	ItBu	0
5	PPh ₃	0
6	PCy ₃	0
7	PBu ₃	0
8	-	0

^aReaction conditions: 5 mol % Ni(COD)₂, 10 mol % ligand, toluene, 60 °C, overnight.^bDetermined by GC using naphthalene as an internal standard.

Table 2Ni-catalyzed rearrangements of vinylaziridines^a

Entry	R	NHC	Product ^c
1	Tr (1a)	IPr	
2	Bz (1b)	IPr	
3	Boc (1c)	IPr	R' = Ph (2b)
4	MeO ₂ C (1d)	IPr	R' = OBU' (2c)
5	CHPh ₂ (1e)	IPr	R' = OMe (2d)
6	CHPh ₂ (1e)	SIPr	
7	Ts (1f)	IPr	
			N. R.

^aReaction conditions: 5 mol % Ni(COD)₂, 10 mol % NHC, toluene, overnight.^cDetermined by ¹H NMR.

Table 3Ni-catalyzed rearrangements of **4a**^a

Entry	L	time (h)	Ratio ^b 5a : 6a : 7a	%Conversion of 4a
1	none	12	-	0
2	PPh ₃	12	-	0
3	PBu ₃	12	-	0
4	IMes	6	1 : 2 : trace	100
5	IPr	2	1 : 1 : trace	100
6	SIPr	6	4 : 1 : trace	100
7	IrBu	2	trace : trace : 1	100

^aReaction conditions: 5 mol % Ni(COD)₂, 10 mol % ligand, C₆D₆, 60 °C.^bDetermined by ¹H-NMR.