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[3+2] Cross-Coupling Reactions of Aziridines with Isocyanates Catalyzed by Nickel(II) Iodide

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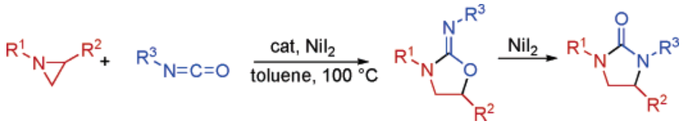
ABSTRACT



Cycloaddition of aziridines with isocyanates proceeded smoothly in the presence of a nickel catalyst, and five iminooxazolidine derivatives were isolated in good yields. The best result was obtained when the reaction was carried out in the presence of NiI_2, and a longer reaction time allowed the isomerization of the iminooxazolidine to the corresponding imidazolidinone derivatives.

Cycloaddition reactions of three-membered heterocycles with heterocumulenes are efficient methods for the synthesis of heterocyclic compounds. For example, $Pd(PhCN)_2Cl_2$ catalyzed the cycloaddition of aziridines and carbodiimides to form imidazolidinimine.[1] The Pd-catalyzed[2−5] or NaI-catalyzed[6−8] reactions of aziridines with phenyl isocyanate have also been reported. In these reactions, imidazolidinones were isolated as the major product. In the cycloaddition of aziridine with carbon dioxide, the Ni(II)[9] complex (electrochemical process) and LiI[10] were efficient catalysts. Organoantimony halides were also capable of catalyzing the cycloadditions of aziridines with heterocumulenes such as carbon dioxide, carbon disulfide, and phenyl isothiocyanate.[11−13] Although a variety of catalysts have been developed, most of the reactions were carried out at high temperature or for a long period. Moreover, there are still few examples of metal-catalyzed cycloaddition reactions involving aziridines with isocyanates. Consequently, we investigated cycloaddition reactions of aziridines with isocyanates in the presence of Ni catalysts.

The reaction of 1-benzylaziridine **1a** with phenyl isocyanate **2a** in the presence of a Ni catalyst proceeded at 100 °C to give the corresponding iminooxazolidine derivative **3aa** and imidazolidinone derivative **4aa**. We examined various Ni catalysts, and the results are summarized in Table 1.

The reaction proceeded slowly in the presence of 10 mol % $Ni(PPh_3)_2Br_2$, and **3aa** and **4aa** were isolated as the major products in 65% combined yield (entry 1). When we used $NiBr_2$ as a catalyst, a higher catalytic activity was observed

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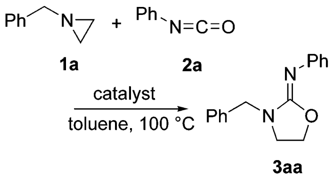
Table 1. Ni-Catalyzed Cross-Coupling Reactions of **1a** with **2a**



entry	catalyst (mol %)	time (h)	yield of **3aa** + **4aa** (%)[a]	ratio (**3**:**4**)[b]
1	$Ni(PPh_3)_2Br_2$ (10)	88	65	5:1
2	$NiBr_2$ (10)	40	70	6:1
3	$Ni(PPh_3)_2I_2$ (10)	16	99	22:1
4	NiI_2 (10)	1.0	92	35:1
5	NiI_2 (1.0)	2.5	95	≫50:1
6	LiI (1.0)	2.5	97	≫50:1
7	TBAI (1.0)	2.5	30[c]	3:1
8	NaI (10)	1.0	6.3[c]	1.5:1
9	no catalyst	3.0	25[c]	6:1

[a] Isolated yield of **3** + **4**. [b] Determined by NMR. [c] Contaminated with a small amount of a byproduct.

(entry 2). The rate as well as selectivity of the reaction improved when the reaction was carried out in the presence of $Ni(PPh_3)_2I_2$ or NiI_2 [14] (entries 3 and 4). The reaction was catalyzed efficiently even in the presence of 1 mol % of NiI_2: the reaction was completed in 2.5 h, and the cycloadduct was isolated in 95% yield (entry 5). We further examined the catalytic activity of other iodides, such as LiI, tetra-*n*-butylammonium iodide, and NaI, and found that LiI was also a good catalyst, whereas other iodides were less efficient (entries 6−8). Although the reaction proceeded slowly even in the absence of the catalyst, the acceleration of the reaction by NiI_2 was obvious (entries 5 and 9).

Though we assumed that Lewis acids could be efficient catalysts for the reaction and we carried out this reaction in the presence of some Lewis acids such as $BF_3{\cdot}OEt_2$, $Ni(OTs)_2$, and $Ni(OTf)_2$, the reaction did not proceed efficiently. As the catalytic activity of LiI[10] was reported in the literature, the high catalytic activity of NiI_2 indicates that the iodide plays an important role for this catalytic reaction.[15] At the same time, however, the countercation seems to have a significant effect on the catalytic activity. Because the unique catalytic activity of NiI_2 was observed in some reactions (vide infra), we selected NiI_2 as the catalyst and carried out further studies.

We also examined the effect of the solvents on the reaction. Although the reaction proceeded smoothly when 1,4-dioxane, DMF, and DMSO were used as the solvents, the best result was obtained when the reaction was carried out in toluene. The structure of **3aa** was analyzed by an X-ray diffraction study, and the iminooxazolidine framework and the *E* configuration of the imine moiety were confirmed (Figure 1).[16]

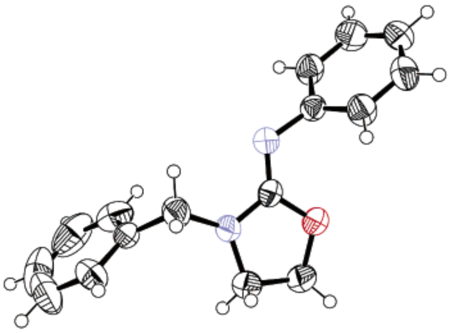
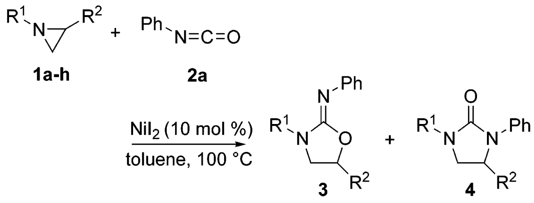


Figure 1. ORTEP view of 1-benzyl-2-phenyliminooxazolidine (**3aa**).

We next examined the reaction of various aziridines in the presence of NiI_2. The iminooxazolidine derivative **3** was isolated as the single or the major product, and the results are summarized in Table 2.

Table 2. NiI_2-Catalyzed Cross-Coupling Reactions of Aziridines (**1a**−**h**) with **2a**



entry	compd	R^1	R^2	time (h)	yield of **3** (%)	yield of **4** (%)
1	**1a**	benzyl	H	1.0	92	
2	**1b**	*n*-butyl	H	1.0	89	
3	**1c**	*t*-butyl	H	0.25	78[a]	5[a]
4	**1d**	$TBSOCH_2CH_2$	H	5.0	75	
5	**1e**	benzyl	Ph	1.0	82	14
6	**1f**	*n*-butyl	Ph	0.5	86	5
7	**1g**	Ph	H	72	20[b]	5
8	**1h**	Ts	H	72		

[a] Determined by NMR. [b] Aziridine did not disappear.

When *n*-butylaziridine **1b**, *tert*-butylaziridine **1c**, and *tert*-butyldimethylsiloxyethylaziridine **1d** were used, the reaction

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[14] Although the reaction proceeded when we carried out the reaction at lower temperature (50 °C or 80 °C), a longer reaction time was required.

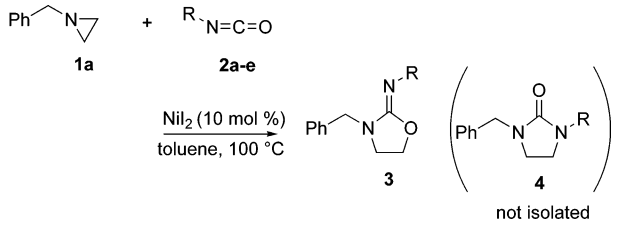
[15] The catalytic activity of Ni(0) complexes such as $Ni(PPh_3)_2(cod)$ and $Ni(PPh_3)_4$ was also very low.

[16] X-ray data were collected on a Bruker Smart1000 CCD detector. The crystal structure was solved by direct methods SHELXS-97 (Sheldrick, 1997) and refined by full-matrix least-squares SHELXL-97 (Sheldrick, 1997). All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included as their calculated positions. Crystal data for **3aa**: $C_{16}H_{16}N_2O$; M = 252.31 g mol^{-1}; monoclinic; $P2_1/n$; colorless prism measuring 0.3 × 0.3 × 0.3 mm; $T = 300$ K; $a = 8.0158(16)$, $b = 6.5155(13)$, $c = 26.090(5)$ Å; $\beta = 90.072(3)°$; $V = 1362.6(5)$ Å^3; $Z = 4$; $D_c = 1.230$ Mg m^{-3}; $\mu = 0.078$ mm^{-1}; $T_{max} = 0.9770$, $T_{min} = 0.9770$, GOF on $F^2 = 0.712$; R1 = 0.0394, wR2 = 0.0825 ([$I > 2\sigma(I)$], R1 = 0.0876, and wR2 = 0.0895 (all data). CCDC-280438.

proceeded smoothly and the corresponding coupling products were isolated in good yields (entries 1−4). However, in the reaction of butylaziridine **1c**, the selectivity of the reaction decreased (entry 3). Disubstituted aziridines such as **1e** and **1f** were also good substrates for the [3+2] coupling reaction, and the corresponding iminooxazolidine derivatives **3** were isolated in good yields (entries 5 and 6). The selective cleavage of the benzylic C−N bond was observed in the reactions of 2-phenyl-substituted aziridines. In these reactions, however, a small amount of **4** was also isolated. When phenylaziridine **1g** was used as the substrate, the progress of the reaction was very sluggish, and the yields of the products were low (entry 7). The cycloaddition reaction did not proceed when tosylaziridine **1h** was selected as the substrate (entry 8).

We also examined the reaction of benzylaziridine **1a** with various isocyanates (Table 3). The reaction of **1a** with benzyl isocyanate **2b** proceeded smoothly, and compound **3ab** was isolated in 74% yield (entry 2). The reaction of other isocyanates also proceeded efficiently, and the products were isolated in high yields (entries 3−5). It is noteworthy that the formation of **4** was not observed in those reactions.

Table 3. NiI_2-Catalyzed Cross-Coupling Reactions of **1a** with Isocyanates (**2a**−**e**)



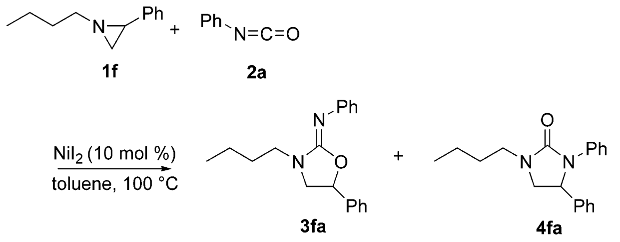
entry	compd	R	time (h)	yield of **3** (%)
1	**2a**	phenyl	1.0	92
2	**2b**	benzyl	3.0	74
3	**2c**	*p*-methoxyphenyl	1.0	78
4	**2d**	*p*-acetylphenyl	1.0	82
5	**2e**	1-naphthyl	1.0	91

During the study, we observed that the ratio of **3** to **4** depended on the reaction time in some experiments. We carried out the reaction of **1f** with **2a** to examine the relationship between the reaction time and the ratio of the products. The results are summarized in Table 4.

When the reaction was carried out for a shorter period (0.5 h), the iminooxazolidine derivative **3fa** was isolated as the major product (entry 1); the yield of **3fa** decreased and that of **4fa** increased to 32% when the reaction time was 4 h (entry 2). The iminooxazolidine **3fa** disappeared, and the imidazolidinone **4fa** was isolated as the major product when the reaction was carried out for 16 h (entry 3).

We hypothesized that **3** isomerized to **4** in the presence of Ni catalysts, and we examined the isomerization of **3fa** (Scheme 1). Although the isomerization of **3fa** did not proceed and **3fa** was recovered unchanged when the reaction was carried out in the absence of NiI_2, the reaction proceeded smoothly in the presence of NiI_2 and **4fa** was isolated in 84% yield. Although the isomerization of **3fa** proceeded in the presence of LiI, the rate of the conversion was slower and a 53:47 mixture of **3fa** and **4fa** was formed (91% total yield) under the same condition. To the best of our knowledge, iminooxazolidine derivatives isomerized to imidazolidinone derivatives at 220−240 °C,[17] and our study revealed that NiI_2 was also an efficient catalyst for the isomerization.

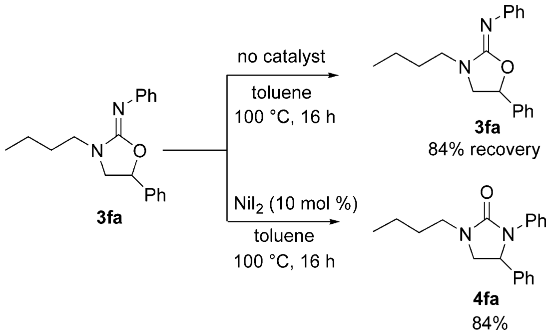
Table 4. Relationship between Reaction Time and Ratio of the Product in the Reaction of **1f** with **2a**



entry	time (h)	yield (%)^a 3fa	yield (%)^a 4fa
1	0.5	86	5
2	4.0	57	32
3	16	0	84

^{a} Isolated yields.

Scheme 1. NiI_2-catalyzed Isomerization of **3fa**



We proposed the mechanism of this reaction as shown in Scheme 2. Thus, NiI_2 would act as a Lewis acid and as an iodide source. The aziridine ring would be cleaved by the nucleophilic attack of the iodide.[10] The selective cleavage of the benzylic C−N bond in the reaction of **1e**−**f** could be explained in terms of the stabilization of the transition state by the phenyl group,[18,19] and similar results have been reported in the literature.[10] A nickel amide **5** would be a

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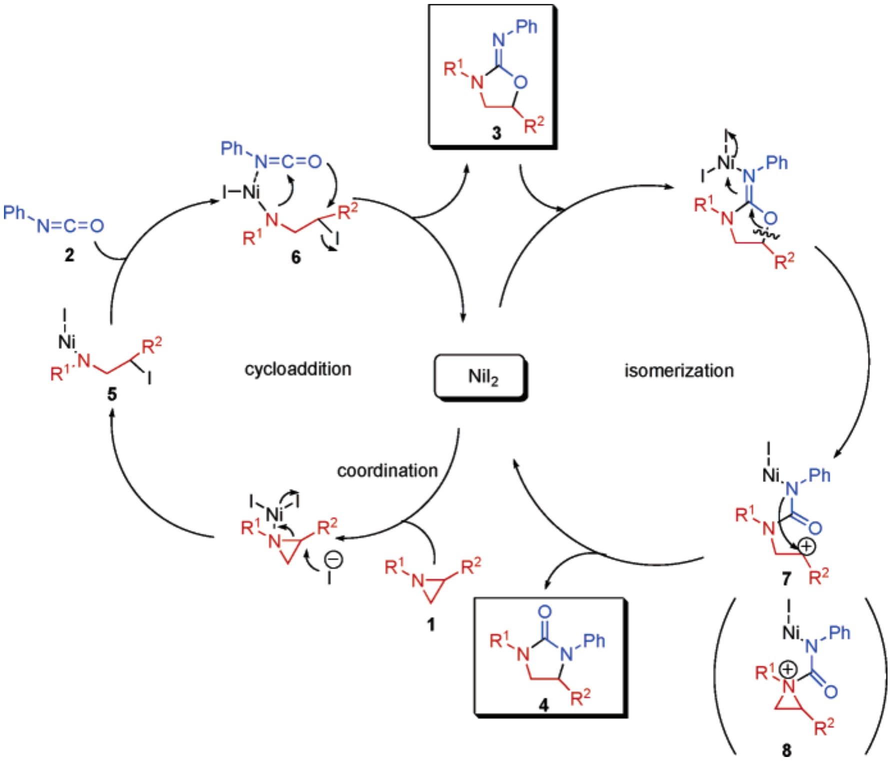
Scheme 2. A Possible Mechanism for the Formation of **3** and **4**



strong nucleophile and would attack the isocyanate **2** to give the iminooxazolidine **3**.

The isomerization of **3** would proceed by the coordination of NiI_2 to the imine moiety of **3**, followed by the cleavage of the C−O bond of **3**.[20] A carbocation **7** or an aziridinium ion **8** would be formed, and the imidazolidinone **4** would be isolated as the final product by the recyclization of the cationic intermediate **7** or **8**.

In summary, we found that the cycloaddition of aziridines with isocyanates proceeded smoothly in the presence of nickel catalysts and five-membered heterocycles were isolated in good to high yields. NiI_2 was a very effective catalyst for the reaction. We also found that iminooxazolidine derivatives isomerized to imidazolidinone derivatives in the presence of NiI_2. The study provided an efficient method for the selective preparation of five-membered heterocycles.

Supporting Information Available: Detailed experimental procedures, spectral data of **3** and **4**, and X-ray crystallographic data (CIF) for **3aa**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Alternatively, the iodide may react as a nucleophile in this process. The stereochemical study of this reaction will distinguish the processes.