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EFFECT OF COPPER(II) TRIFLATE ON INTRAMOLECULAR DIELS-ALDER REACTION OF OXAZOLE-OLEFINS

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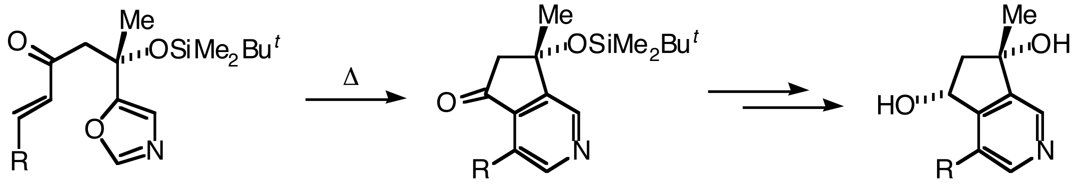
Abstract - Intramolecular Diels-Alder reaction of the oxazole-olefins (**8a**) and (**11a**) was effectively promoted by addition of a catalytic amount of copper(II) triflate to afford the cyclopenta[*c*]pyridines (**9a**) and (**12a**), respectively.

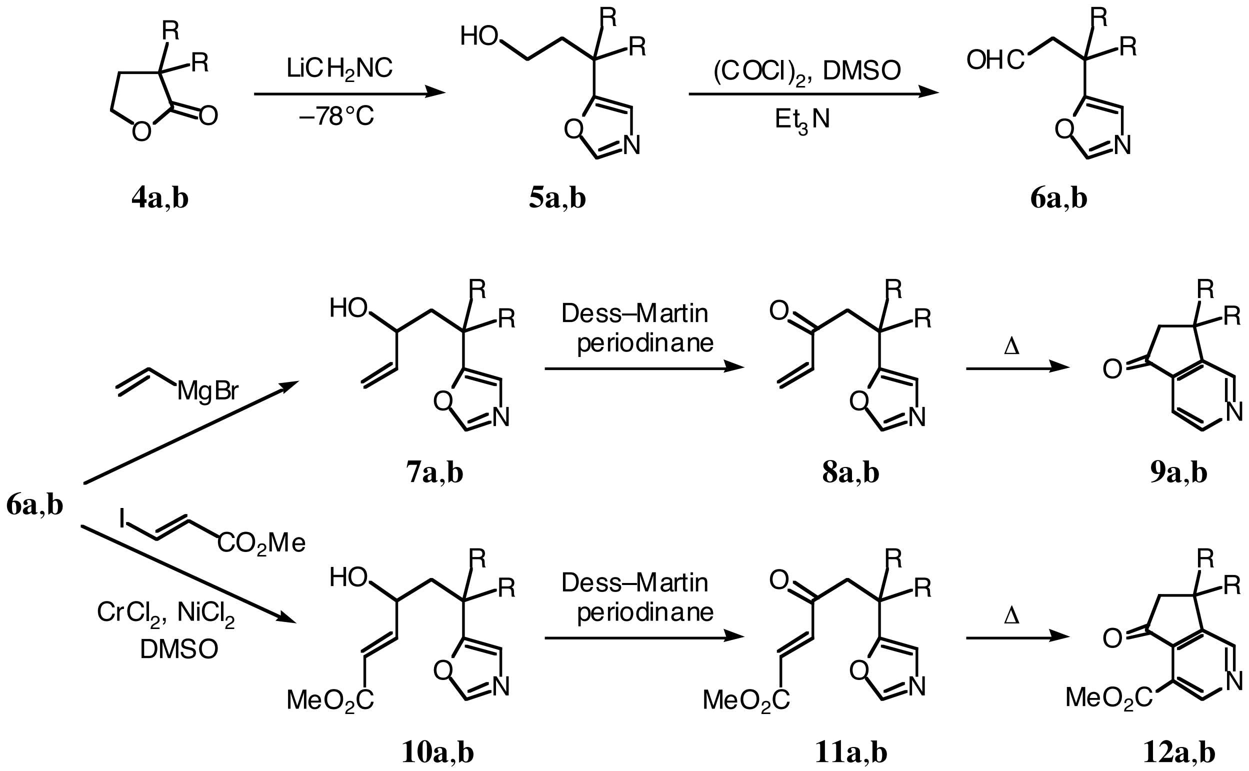
Oxazoles have been known to participate as azadiene components in Diels-Alder reactions with olefinic dienophiles to give pyridine derivatives.[1] Since an intramolecular version of this cycloaddition was reported for the first time by Levin and Weinreb,[2] it has been occasionally used for the synthesis of annulated pyridines.[3] Although we have recently achieved the synthesis of two monoterpene alkaloids, (-)-plectrodorine (**3a**) and (+)-oxerine (**3b**), possessing a cyclopenta[*c*]pyridine ring system, the yields of the intramolecular Diels-Alder reaction of the oxazole-olefins (**1a**,**b**) exploited as a key step of the synthesis were significantly low (**2a**; 37%, **2b**; 23%).[4] This led us to investigate the effect of Lewis acids on the corresponding cycloaddition of the dimethyl substituted derivatives (**8a**) and (**11a**) and the unsubstituted congeners (**8b**) and (**11b**), selected as models for **1a** and **1b**.



1a,**b** **2a**,**b** **3a**,**b**

a: R = CO_2Me, **b**: R = H

The requisite oxazole-olefins (**8a**,**b**) and (**11a**,**b**) were prepared from the lactones (**4a**,**b**) according to our previous procedure for **1a**,**b**.[4] Thus, treatment of α,α-dimethyl-γ-butyrolactone (**4a**)[5] with 2.5 equiv. of α-lithiated methyl isocyanide[6] in THF at –78°C for 3 h, followed by quenching with AcOH provided the oxazole alcohol (**5a**) in 85% yield. After Swern oxidation[7] of **5a** to the oxazole aldehyde (**6a**) in 93% yield, Grignard reaction with vinylmagnesium bromide was performed in THF at –10°C, furnishing the allylic alcohol (**7a**) in 90% yield. The desired **8a** was then readily obtained from **7a** in 85% yield by oxidation with the Dess-Martin periodinane.[8] On the other hand, coupling reaction of **6a** with methyl *trans*-3-iodoacrylate[9] was carried out in DMSO by using $CrCl_2$ and a catalytic amount of $NiCl_2$ according to to Kishi's modification[10] of the Nozaki conditions[11] to afford **10a** (59% yield), which was also converted into **11a** in 86% yield by a similar oxidation. A parallel sequence of reactions starting from γ-butyrolactone (**4b**) and proceeding through the intermediates (**5b**; 89%), (**6b**; 67%), (**7b**; 85%), and (**10b**; 52%) provided the unsubstituted substrates (**8b**; 84%) and (**11b**; 71%).



a: R = Me, **b**: R = H

With four model oxazole-olefins (**8a**,**b**) and (**11a**,**b**) in hand, we first examined the intramolecular Diels-Alder reaction of **8a** in detail. As listed in Table I, heating a 0.05 M solution of **8a** in *o*-dichlorobenzene (*o*-DCB) at 150°C under argon for 24 h provided the cyclopenta[*c*]pyridine (**9a**); the yield, however, was only 21% (Entry 2). Although Weinreb *et al.* used DBN successfully in intramolecular oxazole-olefin Diels-Alder reactions,[2,3b] no formation of **9a** was observed in the presence of the amidine (Entry 3). As the first example of Lewis acid catalysis in oxazole-olefin cycloadditions, Levin recorded the results of investigation on the effect of a europium salt.[3c] In the case of **8a**, however, addition of Eu(fod)$_3$ failed to improve the yield of **9a** (Entry 4). Fortunately, several metal triflates, such as Yb(OTf)$_3$, Sc(OTf)$_3$, and Cu(OTf)$_2$, proved to be effective to carry out the cycloaddition of **8a** (Entries 5-7). The best result was obtained by heating **8a** in *o*-DCB in the presence of 2 mol % of Cu(OTf)$_2$ at 180°C for 1 h; under these conditions, **9a** was produced in 55% yield (Entry 9).

Dramatic rate enhancement was observed for the cycloaddition of **11a** possessing an ester group on the terminal olefin when a catalytic amount of Cu(OTf)$_2$ was employed (Table II). In the absence of the catalyst, **12a** was obtained in only 15% yield together with unaltered **11a** (73%) after 24 h at 150°C (Entry 4), whereas smooth cycloaddition occurred in the presence of 2 mol % of Cu(OTf)$_2$, giving **12a** in 95% yield after 30 min (Entry 6). Addition of Eu(fod)$_3$ again failed to effect any improvement (Entry 5). Under the influence of 10 mol % of $Cu(OTf)_2$, the above reaction proceeded even at a lower temperature (Entries 1 and 3).

TABLE I. Intramolecular Diels-Alder Reactions of **8a**

Entry	Solvent	Additive (mol %)	Temp., °C	Time, h	Yield (%) of **9a**
1	Toluene	$Cu(OTf)_2$ (10)	Reflux	24	26
2	*o*-DCB	—	150	24	21
3	*o*-DCB	DBN (75)	150	2	0
4	*o*-DCB	$Eu(fod)_3$ (10)	150	8	8
5	*o*-DCB	$Yb(OTf)_3$ (10)	150	2	37
6	*o*-DCB	$Sc(OTf)_3$ (10)	150	3	40
7	*o*-DCB	$Cu(OTf)_2$ (10)	150	3	48
8	*o*-DCB	—	180	24	20
9	*o*-DCB	$Cu(OTf)_2$ (2)	180	1	55
10	*o*-DCB	$Cu(OTf)_2$ (10)	180	0.5	52

TABLE II. Intramolecular Diels-Alder Reactions of **11a**

Entry	Solvent	Additive (mol %)	Temp., °C	Time, h	Recovery (%) of **11a**	Yield (%) of **12a**
1	Benzene	$Cu(OTf)_2$ (10)	Reflux	16	27	58
2	Toluene	—	Reflux	24	88	3
3	Toluene	$Cu(OTf)_2$ (10)	Reflux	3	0	93
4	*o*-DCB	—	150	24	73	15
5	*o*-DCB	$Eu(fod)_3$ (10)	150	8	47	6
6	*o*-DCB	$Cu(OTf)_2$ (2)	150	0.5	0	95

Finally, we focused our attention on the intramolecular Diels-Alder reaction of the unsubstituted substrates (**8b**) and (**11b**). As compared with the dimethyl substituted compounds (**8a**) and (**11a**), the cycloaddition of **8b** and **11b** turned out to be apparently slow and less effective (Table III). Thus, heating a 0.05 M solution of **8b** in *o*-DCB at 180°C for 24 h produced **9b** in a poor yield along with unaltered **8b** (30%) (Entry 1). Even in the presence of $Cu(OTf)_2$ (10 mol %), the yield of **9b** remained low after 8 h (Entry 3). Although this cycloaddition was somewhat promoted by introduction of the ester group on the terminal olefin of **8b**, the yield of **12b** was moderate (Entry 5).

In conclusion, it has been clarified that the intramolecular Diels-Alder reactions of **8a** and **11a** are considerably accelerated in the presence of $Cu(OTf)_2$ to provide **9a** and **12a**, respectively, possessing the cyclopenta[*c*]pyridine skeleton, in moderate to excellent yield. The large rate enhancement, namely, the " *gem*-

dimethyl effect," observed for the dimethyl substituted substrates (**8a**) and (**11a**) may be explained in terms of the "reactive rotamer effect" described by Jung.[12]

TABLE III. Intramolecular Diels-Alder Reactions of **8b** and **11b** in *o*-DCB

Entry	Substrate	Additive (mol %)	Temp., °C	Time, h	Product	Yield, %
1	**8b**	—	180	24	**9b**	6
2	**8b**	$Sc(OTf)_3$ (10)	180	8	**9b**	15
3	**8b**	$Cu(OTf)_2$ (10)	180	8	**9b**	24
4	**11b**	$Cu(OTf)_2$ (10)	150	4	**12b**	19
5	**11b**	$Cu(OTf)_2$ (2)	180	2	**12b**	42
6	**11b**	$Cu(OTf)_2$ (10)	180	1	**12b**	28

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