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AN EFFICIENT PREPARATION OF 3-AZABICYCLO [3.3.0]-OCT-5-EN-7-ONES FROM PROPARGYL ALCOHOL- COBALT COMPLEXES VIA NICHOLAS REACTION WITH AMIDIC NITROGEN NUCLEOPHILES FOLLOWED BY PAUSON-KHAND CYCLIZATION

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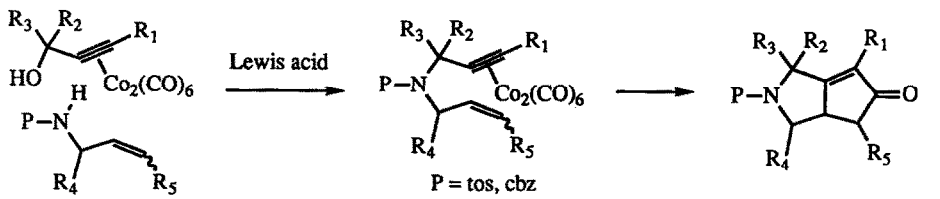
Summary ; 3-Azabicyclo [3.3.0]-oct-5-en-7-ones were efficiently prepared from cobalt-propagyl alcohol complexes and various allyl amides via Nicholas reaction in the presence of $BF_3{\cdot}Et_2O$ followed by Pauson-Khand cyclization promoted with trimethylamine N-oxide or SiO_2.

Cobalt-alkyne complexes have shown the great versatility in synthetic organic chemistry. There are a couple of major applications employing cobalt-alkyne complexes beyond the usage as protected alkynes. One is cycloaddition with alkenes and carbon monoxide to give cyclopentenones, known as Pauson-Khand reaction[1] and the other is the nucleophilic addition to cobalt-complexed propargylic cation, known as Nicholas reaction.[2]

Although there are numerous examples of the preparation of carbobicyclic and oxabicyclic systems from the corresponding carbon and oxygen bridged enyne substrates via Pauson-Khand reaction and their applications to natural products synthesis,[3] nitrogen analogs remained largely unexplored.[4] By the time, we realized these azabicyclic compounds are interesting substances as they are and as synthetic intermediates for some natural products. Thus, we devised a highly efficient one-pot strategy for the preparation of such compounds via Nicholas reaction with amidic nitrogen nucleophiles followed by Pauson-Khand reaction as illustrated in Scheme 1.



Scheme 1

Nicholas reactions with nitrogen nucleophiles are rarely known at present. As far as we are aware, only one example of N-propargylation, a varient of Ritter reaction, was reported from cobalt propargyl alcohol complex and acetonitrile in the presence of mineral acids.[5]

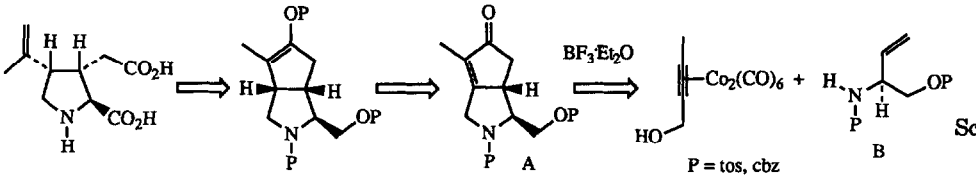
In this letter, we would like to report our findings of facile N-propargylation of various amides and further manipulation, in the case of allyl amides, leading to 3-azabicyclo [3.3.0]-oct-5-en-7-ones. First, we examined the propargylation of various amidic functionalities with a primary propargylic alcohol-cobalt complex. Tosyl amide and Cbz-amide provided an efficient propargylation in the presence

of $BF_3{\cdot}Et_2O$, while t-Boc, benzoyl, and trifluoroacetamide yielded none of propargylated products. Even changing of acids from $BF_3{\cdot}Et_2O$ to $HBF_4{\cdot}Me_2O$ did not provide any beneficial effects for the inert amides but makes the reaction a little bit unfavorable even with tosyl amide.

After completion of N-propargylation, the reaction mixture was quenched with triethylamine and then was subjected to Pauson-Khand reation employing trimethylamine N-oxide[5] or silica gel [3j,k] under oxygen without purification step, thus providing a high efficiency of this one-pot procedure. For example, in the case of allyl tosylamide, the bicyclic compound (entry 1) was obtained in 85% yield. A Cbz-protected amine also worked effectively to provide the corresponding product in 55% yield (entry 2). The presence of oxygen in this reaction with terminal alkynes turned out to be crucial. Under the inert atmosphere, the coupling reaction of aza-bridged enynes yielded a mixture of the proposed product along with a saturated ketone in variable ratio.[7] Disubstituted propargyl alcohol-cobalt complexes provided almost equivalent results to monosubstituted complexes without any complications of the formation of the saturated ketones even under the inert atmosphere (entry 3,4). Disubstituted allyl tosyl amides also provided good yields (entry 5, 6).

More substitution on propargyl carbon on the cobalt-propargyl cation would provide the extra stabilization and one might expect a better N-propargylation. Furthermore, specially in this case, there is no worry about allenic formation via allylic rearrangement as a potential side product.[8] On the other hand, steric hindrances by congestion on propargyl carbon would retard the approach of nucleophiles. This balance has played as a determing factor of reaction pathway and been demonstrated as shown in entry 6,7 and 8 in Table. Under the same reaction condition as previous, butyne-3-ol-cobalt complex generated the corresponding bicyclic compounds in excellent yield, better than the primary propargyl complexes (90% yield from allyl tosylamide with 2:1 diastereoselectivity and 77% yield from allyl-cbz-amide with same diastereoselectivity). However, 3-methyl-1-butyne-3-ol-cobalt complex was totally reluctant to N-propargylation.

Meantime, we envisioned this one-pot procedure would provide a versatile and efficient synthetic route to optically active α-kainic acid and its analogs[9] as shown in Scheme 2.



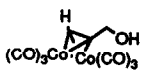
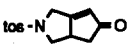
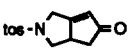
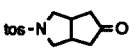
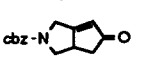
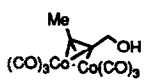
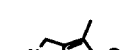
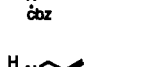
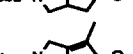
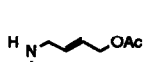
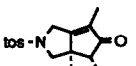
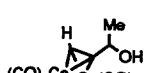
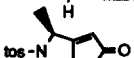
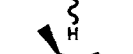
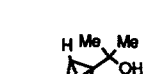
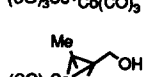
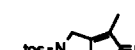
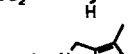
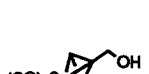
Scheme 2

First, we have examined diastereoselectivity in the key reaction with various protection groups on B [10] (entry 10-13). Under the condition with trimethylamine N-oxide, the reaction provided poor diastereoselectivity (*cis:trans*=2:1) regardless of the protection groups. [11] However, the great enhancement of diastereoselectivity was achieved with a substrate containing MOM protection group for hydroxyl [12] (entry 13) by switching of promotor for the cyclization condition from trimethylamine N-oxide to silica gel. [3j, k, 13]

In conclusion, we have devised an one-pot preparation of 3-azabicyclo [3,3,0]-oct-5-en-7ones from propargyl alcohol-cobalt complexes and allyl amides in high efficiency by the combination of Nicholas reaction and Pauson-Khand reaction.

A representative experimental procedure employing trimethylamine N-oxide is given as follow ;

Table; Examples of one-pot preparations of 3-azabicyclo-[3.3.0]-oct-5-en-7-ones

propargyl-cobalt complex	entry	allyl amide	condition	product		yield[a]
	1		A (B)			85% (70%)
			C			80% (4:1)
	2		A			55%
	3		A			90%
	4		A			69%
	5		A			63%
	6		A			50%
	7		A		*cis* : *trans* = 2 : 1	90%
	8		A		*cis* : *trans* = 2 : 1	77%
	9		A	no propagylation		
	10		A		*cis* : *trans* = 2 : 1	35%
	11		A		*cis* : *trans* = 2 : 1	34%
			(D)		(*cis* : *trans* = 2 : 1)	(35%)
	12		A		*cis* : *trans* = 2 : 1	40%
	13		D		*cis* : *trans* = 6 : 1	50%
	14		A		*cis* : *trans* = 4 : 1	58%

Reaction Conditions; A. 1. $BF_3{\cdot}Et_2O$/ CH_2Cl_2, -78°C - rt, 2. trimethylamine N-oxide (3-4 eq.)/ O_2/ CH_2Cl_2, rt, 1hr.
B. 1. $HBF_4{\cdot}Me_2O$/ CH_2Cl_2, -78°C - rt, 30 min, 2. trimethylamine N-oxide (3-4 eq.)/ O_2/ CH_2Cl_2, rt, 1hr.
C. 1. $BF_3{\cdot}Et_2O$/ CH_2Cl_2, -78°C - rt, 2. trimethylamine N-oxide (3-4 eq.)/ Ar/ CH_2Cl_2, rt, 1hr.
D. 1. $BF_3{\cdot}Et_2O$/ CH_2Cl_2, -78°C - rt, 2. SiO_2, 50°C, 30 min.

a. Yields were calculated based on allyl amides.

To a solution of 3-butyne-2-ol Co complex (2.0g, 5.6mmol) in CH_2Cl_2 (10mL) was added BF_3Et_2O(1.04mL, 8.4mmol) at -78°C under argon. After 10min at -78°C,[14] a solution of N-allyl tosyl amide (1.18g, 5.6mmol) in CH_2Cl_2 (2mL) was introduced. The resulting reaction mixture was allowed to warm to rt and stirred for 30min. The reaction mixture was quenched by Et_3N (10 mmol) and flushed with O_2 for several minutes. To the crude propargylated product in dichloromethane was added trimethylamine N-oxide (5.18 g, 16.8 mmol) in one portion at 0°C. The mixture was stirred at rt for 1h, at which time purple precipitates had formed. The mixture was passed through a small plug of silica gel and the filtrate was concentrated *in vacuo* and purified by silica gel chromatography to give the bicyclic product (1.58 g, 4.5 mmol, 90% yield). [15]

References and Notes

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5. Jeong,N.; Chung,Y.K.; Lee,B.Y.; Lee,S.H.; Yoo,S.-e. *Synlett* **1991**, in press. We have found Pauson-Khand reaction was greatly promoted by trimethylamine N-oxide and presence of oxygen could eliminate minor complications. Similar observations employing N-methylmorpholine N-oxide obtained by Schreiber and coworkers have been reported in this Letter recently (**1990**, *31*, 5289) and this modification could be used for this reaction also.
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10. For the preparation of the optically pure vinyl glycine, Hanessian, S.; Sahoo, S.P. *Tetrahedron Lett.* **1984**, *25*, 1425. for the racemic one see, Vyas, D.M.; Ching,Y,; Doyle,T.W. *J.Org.Chem.* **1984**, *49*, 2037, We have employed racemic vinyl glycine in this study for the determination of diastereoselectivity.
11. Usually trialkylamine N-oxide accelerated the cyclization too much to give a good stereoselectivity. For example, the reaction between alkyne-cobalt complex and norbornadiene gave a mixture of *exo* and *endo* (*ca* 85:15) products under this condition, while thermal reaction afforded an *exo* product exclusively. Refer ref 5.
12. Magnus, P.; Principe, L.M. *Tetrahedron Lett.* **1985**, *26*, 4851. No good reasons for the beneficial effects of MOM groups are provided yet.
13. Completion of the total synthesis starting with the optically active vinyl glycine is in progress and will be published elsewhere.
14. At this stage, bishexacarbonyldicobaltacetylene ether (^{1}H NMR (C_6D_6); d. 1.10 (6 H, d, J = 6.3Hz), 2.80 (2 H, m), 5.5 (2 H, br s)) was formed (R_f= 0.7 compared to R_f=0.3 for the propargyl alcohol-cobalt compex in hexane-ethyl acetate= 2:1), which was purified and characterized but subjected to the nucleophilic addition with amides directly.

15. N.J.,S.H.L., S.J.L., S.-e.Y. thank the Ministry of Science and Technology of Korea for financial support and Y.K.C. thanks the Ministry of Education of Korea for financial support through the Basic Sicence Research Institute Program(1990).

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