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Synthesis of α-Vinylidene-β-Lactams by the Palladium-Catalyzed Carbonylation of 4-Amino-2-alkynyl Carbonates

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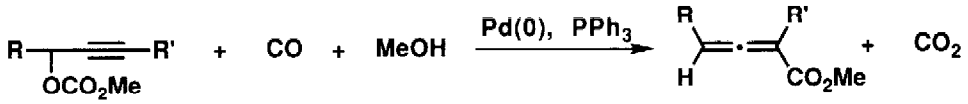
Key words

4-ethyl-2,6,7-trioxo-1-phosphabicyclo [2.2.2]octane, α-vinylidene-β–lactams, palladium-catalyzed carbonylation of 4-amino-2-alkynyl carbonates

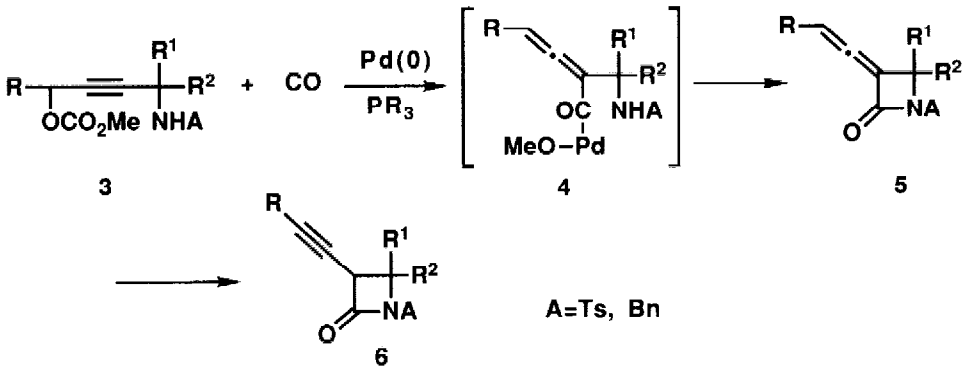
Abstract: The palladium catallyzed carbonylation of 4-amino-2-alkynyl carbonates proceeded under mild conditions to afford α-vinylidene-β-lactams in moderate yields. The cyclic phosphite, 4-ethyl-2,6,7-trioxa-1-phosphabicyclo[2.2.2]octane was found to be the best ligand.

Discovery of new efficient synthetic methods for β-lactams is an important problem, although numerous methods have been reported alrcady.[1] One interesting possibility is the application of various transition metal compounds as reagents and several methods are known.[2] Among them, particularly useful is catalytic reactions. One typical example is the palladium-catalyzed carbonylation of 2-bromoallylamine derivatives to afford α-methylene-β–lactams.[3] We reported before the facile palladium-catalyzed carbonylation of 2-alkynyl carbonates(propargyl carbonates) **1** to afford 2,3-alkadienoates **2** in good yields.[4]



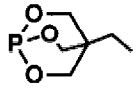
1 **2**

We wanted to apply this facile carbonylation to the synthesis of β-lactams by introducing an amino group to 2-alkynyl carbonates, expecting the formation of α-vinylidene-β–lactams. In this paper we wish to report the carbonylation of 4-amino-2-alkynyl carbonates **3** to form α-vinylidene-β–lactams **5**. The reaction can be expressed by the following general scheme. α-Vinylidene-β-lactam **5** is the primary product of the carbonylation. But, depending on the reaction conditions, complete isomerization of the α-vinylidene group to the acetylene takes place, and in some cases, the α-alkynyl-β-lactams **6** were isolated as sole products.



3 4 5 6

After surveying the reaction conditions, particularly the effect of the ligands, we found that the carbonylation can be carried out smoothly by using 4-ethyl-2,6,7-trioxa-1-phosphabicyclo[2.2.2]octane (7) as the ligand.

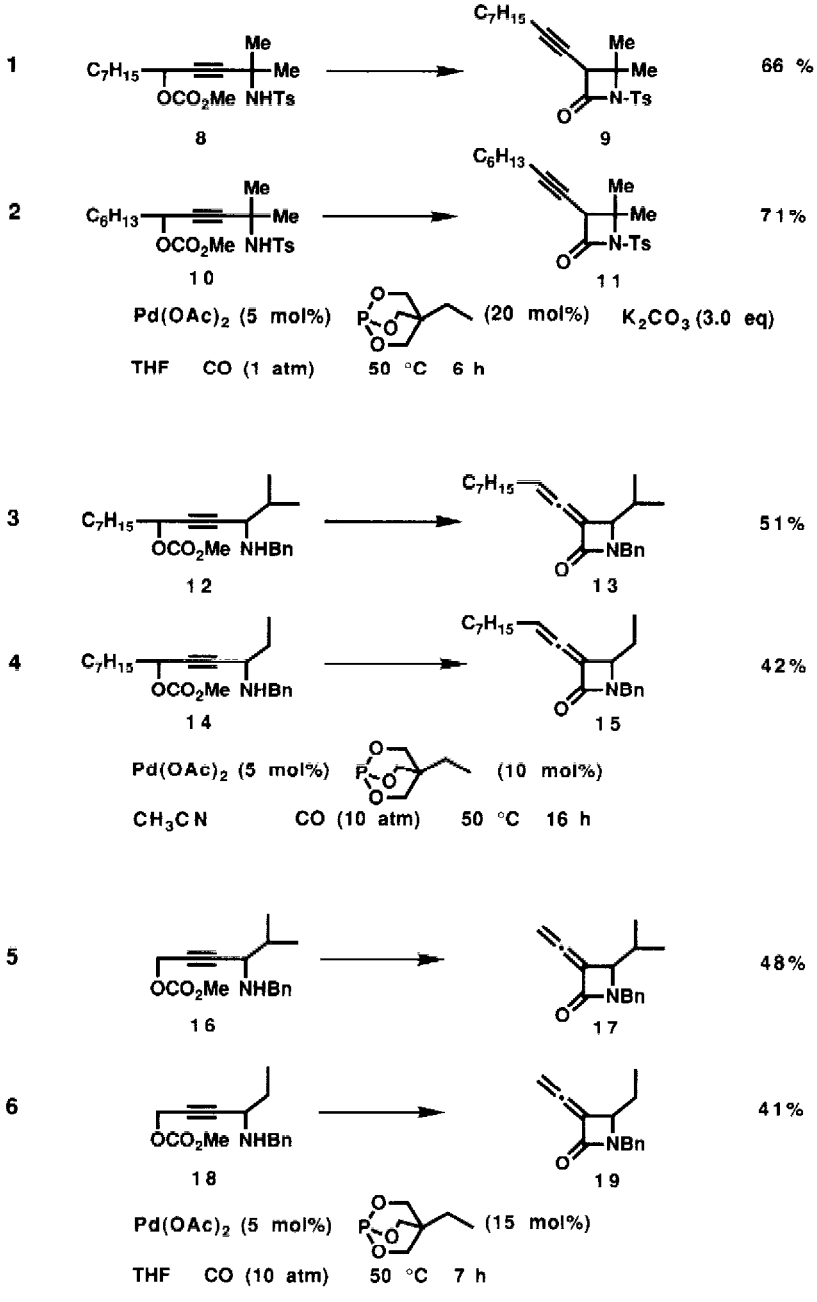


7

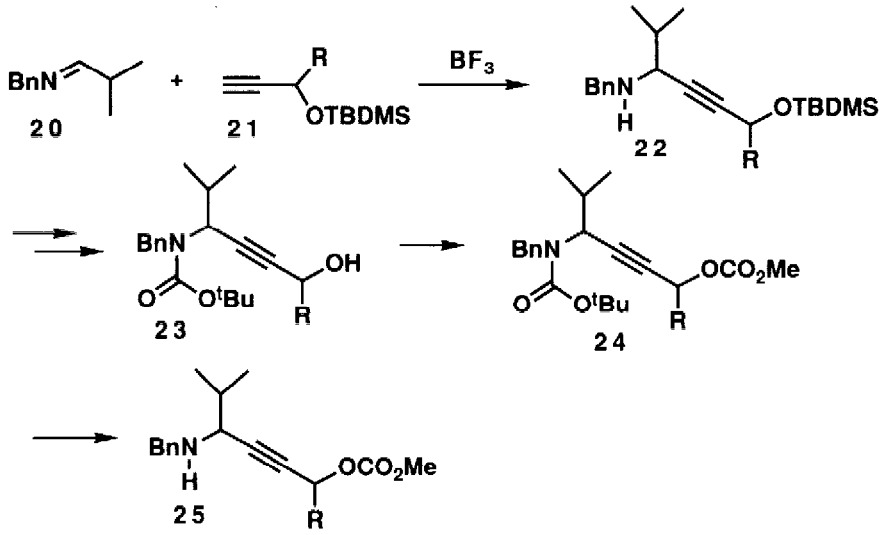
Any alkyl group can be introduced as the R, R^1, and R^2 groups in **3**. When R is hydrogen, the α-vinylidene group without a substituent can be synthesized. As the protecting groups A of the amine, both electron-withdrawing groups such as p-toluenesulfonyl (Ts) group, and electron-donating groups such as benzyl group can be used satisfactorily. The reaction of the tosyl protected amine should be carried out in the presence of potassium carbonate, without which the yield was lower. The addition of potassium carbonate was not necessary for the carbonylation of the benzyl protected amine. The carbonylation proceeded in THF or acetonitrile at 50°C even under atmospheric pressure or 10 atm of carbon monoxide. The isomerization of the α–vinylidene group to acetylene took place particularly in the presence of potassium carbonate. The yields of the β–lactams were good to moderate. It seems likely that the unsubstituted α-vinylidene group is not a stable functional group particularly in the presence of the palladium catalyst. This is why only moderate yields were obtained when R = H. (entries 5 and 6) The results of the β–lactam formation with various substituents are shown in Table 1. The mechanism of the β-lactam formation can be explained by the formation of the allenylpalladium complex as an intermediate, which undergoes carbon monoxide insertion to form the acylpalladium complex **4**. Then the intramolecular attack of the amino group to the acylpalladium affords the β-lactam.

A typical procedure is the following (entry 1 in Table 1). In a round-bottomed flask were added palladium acetate(6 mg, 5 mol%), the cyclic phosphite(17 mg, 20 mol%) and potassium carbonate (1.5 mmol) in THF (1 ml). Then 1-heptyl-4-toluenesulfonylamino-4-methylpentynyl methyl carbonate **8** (0.5 mmol) in THF (2 ml) was added. The reaction was carried out at 50°C under atmosphere of carbon monoxide (a rubber balloon filled with carbon monoxide was attached) for 7.5 hr. After the usual work-up, the β–lactam **9** was isolated (126 mg, 66%) as an oil, which showed the following analytical and spectral data. Anal. Calcd. for $C_{21}H_{29}O_3NS$: C, 67.17; H, 7.78; N, 3.73. Found: C, 67.39; H, 7.96; N, 3.94. IR spectrum (neat); 1795, 1785 cm^{-1}, NMR(^{13}C): δ 89.9, 102.3, 127.3, 129.9, 136.8, 145.1, 161.0.

Table 1


1
C7H15
Me
Me
OCO2Me NHTs
8
C7H15
Me
Me
N-Ts
O
9
66 %
2
C6H13
Me
Me
OCO2Me NHTs
10
C6H13
Me
Me
N-Ts
O
11
71%
Pd(OAc)2 (5 mol%)
(20 mol%)
K2CO3 (3.0 eq)
THF CO (1 atm) 50 °C 6 h
3
C7H15
OCO2Me NHBn
12
C7H15
NBn
O
13
51%
4
C7H15
OCO2Me NHBn
14
C7H15
NBn
O
15
42%
Pd(OAc)2 (5 mol%)
(10 mol%)
CH3CN CO (10 atm) 50 °C 16 h
5
OCO2Me NHBn
16
NBn
O
17
48%
6
OCO2Me NHBn
18
NBn
O
19
41%
Pd(OAc)2 (5 mol%)
(15 mol%)
THF CO (10 atm) 50 °C 7 h

The 4-amino-2-alkynyl carbonates **8** and **10** (entries 1 and 2 in Table 1) were prepared from commercially available 1,1-dimethylpropargylamine. Also, the 4-amino-2-alkynyl carbonates **12, 14, 16, 18** (entries 3-6 in Table 1) were prepared by the sequence of reactions shown below. Following the reported procedure,[5] O-silyl-protected 4-amino-2-alkyn-1-ols **22** were prepared by the the addition of lithium acetylide derived from silyl-protected propargyl alcohols **21** to aldimines **20** in the presence of BF_3 etherate. The amino group was protected. Then the silyl group was removed to give **23,** and the generated alcohol was treated with ethyl Grignard reagent and converted to carbonates **24** by the reaction of methyl chloroformate. Finally the protection of the amine was removed to afford **25.**



The α-vinylidene β lactams were prepared by other method,[6] and it is known that they have interesting medicinal activity. The carbonylation reaction reported in this paper offers the more convenient synthetic method for this type of β-lactams. Also it is expected that the α-vinylidene-β-lactams prepared by the present method can be converted to the more useful carbapenem derivatives. Further studies on the application of this carbonylation is under active investigation.

References.

1. Recent review, Hart, D. J., Deck-Chan, H., *Chem. Rev.*, **1989,** 89, 1447.
2. Barrett, A. G., Sturgess, M. A., *Tetrahedron*, **1988,** 44, 5615.
3. Chiba, K., Mori, M., Ban, Y., *Tetrahedron*, **1980**, 41, 387.
4 Tsuji, J., Sugiura, T., Minami, I., *Tetrahedron Lett.*, **1986**, 27, 731.
5. Wada, M., Sakurai, Y., Akiba, K., *Tetrahedron Lett.*, **1984,** 25, 1083.
6. Buynak, J. D., Mathew, J., Rao, M. N., Haley, E., George, C., Siriwardane, U., *J . Chem. Soc., Chem. Commun.*, **1987**, 735. Buynak, J. D., Borate, H. B., Husting, C., Hurd, T., Vallabh, J., Mathew, J., Lambert, J., Siriwardane, U., *Tetrahedron Lett.*, **1988**, 29, 5053.

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