A NOVEL SYNTHESIS OF 1,3-BENZODIAZEPIN-2-ONES USING INTRAMOLECULAR HECK REACTION

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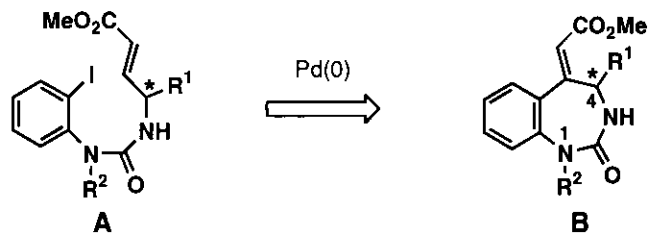
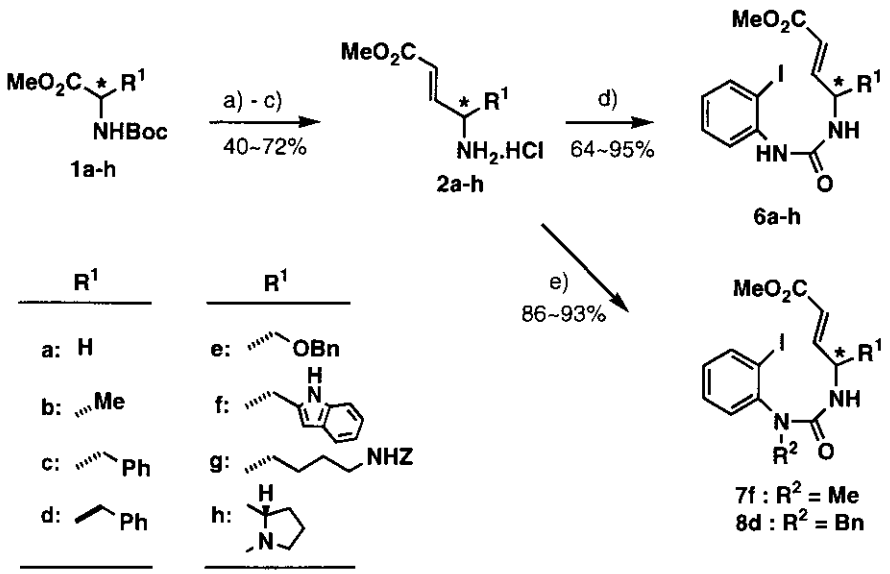
Abstract- The formation of the skeleton of 1,3-benzodiazepin-2-one could be efficiently achieved by intramolecular Heck reaction. This methodology was well applicable to the preparation of optically pure 4-substituted 1,3-benzodiazepin-2-ones starting from easily available α-amino acids.

In recent years, transition metal catalyzed reactions have become great synthetic tools in organic syntheses. In particular, palladium catalyzed reactions[1] have been investigated in detail and used extensively for construction of nitrogen-containing heterocycles[2] such as tetrahydroisoquinolines and benzazepines. In the course of our synthetic studies on extensive search for biologically active compounds, we needed to develop the general synthetic method of 1,3-benzodiazepines. To the best of our knowledge, only a few methods for construction of the skeleton involving conventional formation of cyclic ureas have been reported so far,[3] which have limits in obtaining functionalized 1,3-benzodiazepin-2-ones. This is a sharp contrast to intensive research of 1,4-benzodiazepines[4] from both a synthetic and pharmacological viewpoints. In this communication, we wish to report a novel synthetic method of 1,3-benzodiazepin-2-ones **B** including optically pure C(4)-substitutents from acyclic urea **A** using intramolecular Heck reaction as a key step.



A **B**

First of all, we prepared the substrate **A** starting from α-amino acids for the Heck reaction as follows (Scheme 1). The amino aldehydes obtained in a usual way[5] from the protected α-amino acids (**1a-h**) were subjected to the Wittig olefination followed by acid treatment to give the corresponding *trans*-4-aminocrotonates (**2a-h**) predominantly.[6] The amines (**2a-h**) thus obtained reacted with the 2-iodophenyl isocyanate resulted by the Curtius rearrangement of 2-iodobenzoic acid (**3**) in the presense of DPPA(diphenylphosphoryl azide) to afford the corresponding ureas (**6a-h**) in good yields.[7]



Conditions: a) DIBAL-H(1.5 eq), toluene, -78°C, or 1) LiCl(2 eq), $NaBH_4$(2 eq), THF-EtOH, rt, 2) SO_3.Py(3 eq), Et_3N(3 eq), DMSO-CH_2Cl_2,-20~-10°C; b) $Ph_3P{=}CHCO_2Me$(1.2 eq), toluene, rt; c) 4N-HCl, dioxane, 0°C; d) 2-Iodobenzoic acid **3** (1.0 eq), DPPA(1.1 eq), Et_3N(2.1 eq), benzene, reflux; e) *N*-Methyl-2-iodoaniline **4** (1.0 eq) or *N*-benzyl-2-iodoaniline **5** (1.0 eq), triphosgene, Et_3N, CH_2Cl_2, -10°C~rt.

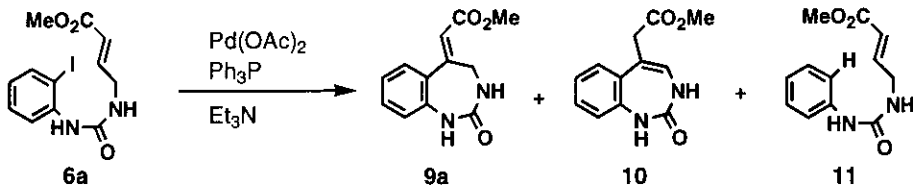
Scheme 1

N-Alkylated ureas (**7f**) and (**8d**) were easily obtained by the treatment of the amines (**2f**) and (**2d**) with imidoyl chlorides[8] derived from *N*-methyl-2-iodoaniline (**4**) and *N*-benzyl-2-iodoaniline (**5**) respectively.

With the substrates (**6-8**) in hand, we focused on the investigation of reaction conditions of the intramolecular Heck reaction using **6a**. After several attempts,[9] we found that 1,3-benzodiazepin-2-one (**9a**) with (*Z*)-*exo*-olefin[10] was obtained as a main product in 76% yield, by treatment with $Pd(OAc)_2$(10 mol%), Ph_3P(20 mol%), Et_3N(1.5 eq) in refluxing THF for 4 h, together with the olefin isomerization product (**10**) (9%) and the deiodinated product (**11**) (14%) (Table 1, Entry 3). The main formation of **9a** with (*Z*)-*exo*-olefin showed that this intramolecular Heck reaction proceeded with *syn* addition of primarily formed Pd-aryl species on intramolecular C-C double bond followed by *syn* elimination of Pd-H.[11]

Under the same conditons, other substrates (**6b-h, 7f** and **8d**) obtained from α–amino acids were also transformed to the desired 1,3-benzodiazepin-2-ones (**9b-h, 13f** and **14d**) in high yields as shown in Table 2. In these reactions, unlike the case of **6a** (Entry 1), any side products such as the olefin isomerization products and the deiodinated products were not detected. The presence of 4-substituents or *N*-substituents might bring about preferable conformation in the transition state to promote the cyclization. It should be also noted that these cyclization reactions cleanly proceeded without any epimerization at C(4) center. This was unambiguously confirmed by use of chiral HPLC analysis on the Heck reaction products (**9c**) and (**9d**) derived from (*S*)-phenylalanine and (*R*)-phenylalanine respectively.[12]

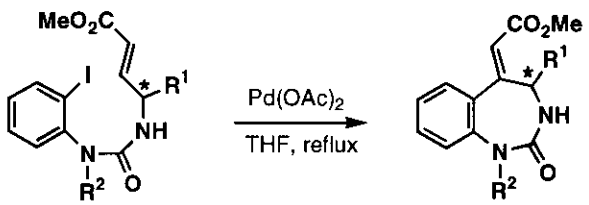
Table 1. Optimization of Intramolecular Heck Reaction



Entry	$Pd(OAc)_2$ (mol%)	Ph_3P (mol%)	Et_3N (eq)	Solvent	Condition	Product Yield (%)[a]		
						9a	**10**	**11**
1	1	2	1.5	THF	reflux, 60 h	32	20	-[b]
2	5	10	1.5	THF	reflux,16 h	74	11	12
3	10	20	1.5	THF	reflux, 4 h	76	9	14
4	2	4	1.3	DMF	100°C, 3 h	18	-[b]	-[b]
5	10	20	1.3	DMF	100°C, 2 h	43	-[b]	-[b]

a: Isolated yields b: Not isolated

Table 2. Intramolecular Heck Reactions

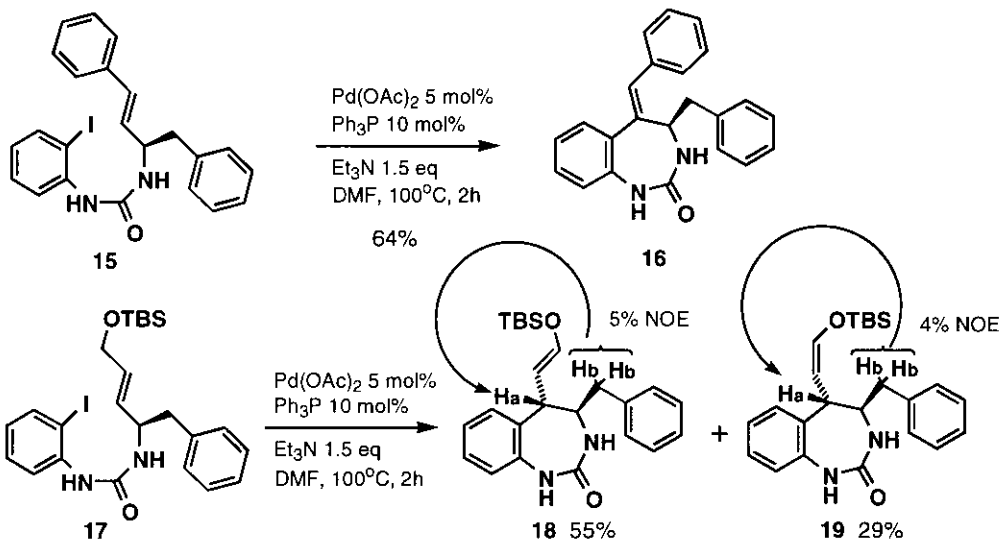


Entry	Substrate	Condition[a]	Product (yield:%)[b]
1	**6a**	A	**9a** (76)
2	**6b**	A	**9b** (89)
3	**6c**	A	**9c** (95)
4	**6d**	A	**9d** (96)
5	**6e**	A	**9e** (89)
6	**6f**	A	**9f** (89)
7	**6g**	A	**9g** (100)
8	**6h**	A	**9h** (100)
9	**7f**	B	**13f** (72)
10	**8d**	B	**14d** (79)

a: Condition A : $Pd(OAc)_2$ 5 mol%, Ph_3P 10 mol% , Et_3N 1.5 eq
Condition B : $Pd(OAc)_2$ 10 mol%, Ph_3P 20 mol% , Et_3N 1.5 eq

b: Isolated yield

This methodology could be further extended to the benzylidene derivative (**15**)[13] and alkylidene derivative (**17**)[14] to afford the desired 1,3-benzodiazepin-2-ones (**16**) and a mixture of **18** and **19**,[15] respectively, as shown in Scheme 2. About the stereochemistry of **18** and **19**, we assumed to be *trans* conformation at C(4) and C(5) substituents on 1,3-benzodiazepine ring of **18** and **19** based on Tietze's report[2] which explained that the π-face selectivity of olefin coordination in Heck cyclization was very high on the influence of the bulkiness of allylic substituent. This might be also supported by the observation of the NOE between Ha and Hb in each product.



Scheme 2

In summary, we established the concise synthetic method of functionalized 1,3-benzodiazepin-2-ones, especially enantiomerically pure 4-substituted 1,3-benzodiazepin-2-ones, using the intramolecular Heck reaction.

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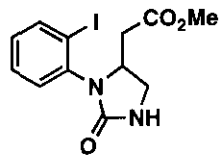
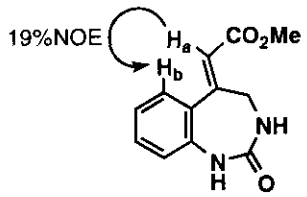
9. The reactivity of this reaction considerably depended on the solvents and bases as follows. When polar aprotic solvents such as DMF, DMSO and MeCN were used, the starting material (**6a**) was consumed very fast within one hour but byproducts (**10**) and (**11**) increased. As shown in Entries 4, 5 of Table 1, the yield of desired product (**9a**) performed in DMF was apparently lower compared to those performed in THF, which showed THF to be the best solvent. Additionally **6a** was insoluble in nonpolar solvent such as toluene and the reaction was not completed. With weak bases such as pyridine, AcONa and Ag_2CO_3, the reaction underwent very slowly. On the other hand, use of strong bases such as DBU and K_2CO_3 increased the Michael product (**12**).



12

10. The geometry of **9a** was determined to be (*Z*)-form because 19% NOE was observed between Ha and Hb.



9a

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12. HPLC conditions: CHIRALCEL OJ (17% hexane/2-propanol(v/v)); Optical rotations, **9c**: $[\alpha]_D^{32}$ -255.2° (c 1.05, dioxane), **9d:** $[\alpha]_D^{32}$ +257.7° (c 1.05, dioxane).
13. Synthesis of **15**: The aldehyde derived from **1d** was subjected to Wittig olefination with benzylidene-triphenylphosphorane in THF followed by same reaction condition as shown in Scheme 1 to give **15** (25% yield from **1d**).
14. Synthesis of **17**: Methyl *N*-Boc-4-aminocrotonate derived from **1d** was subjected to DIBAL-H reduction followed by Curtius rearrangement of **3** to give urea alcohol, which was protected with TBSCl to afford **17** (8% yield from **1d**).
15. The geometry of **18** was determined to be (*E*)-form because of the coupling constant $J_{H\text{-}H}$=11.9 Hz between vinyl protons, and that of **19** was determined to be (*Z*)-form because of $J_{H\text{-}H}$=5.8 Hz.

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