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Aminocarbonylation route to tolvaptan

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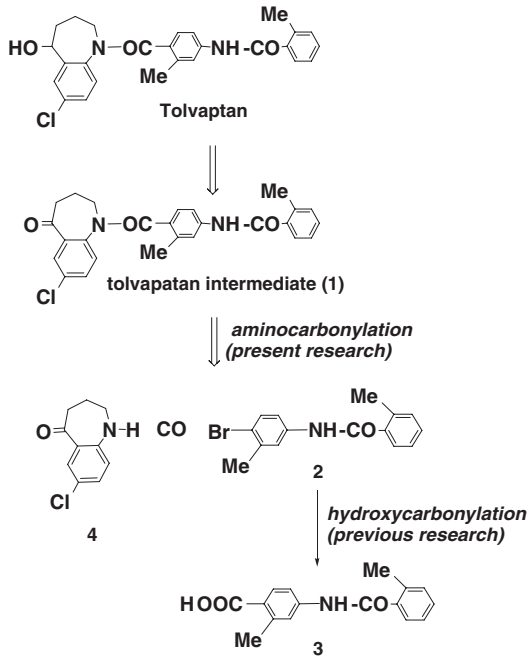
Abstract—Pd-catalyzed aminocarbonylation between aryl bromide and *N*H-benzazepinone was effectively carried out to furnish the key intermediate for tolvaptan (up to 85%) in one step.

Tolvaptan is in clinical trial as an orally active vasopressin (V_2) antagonist,[1] possessing the key benzazepinone amide structural unit, like other congeners of interest.[2] Under these circumstances, construction of the key amide structural units [ArNH–COAr′] by non-conventional method has become major concern in our research process. We would like to describe herein a synthesis of the tolvapatan intermediate **1** (Scheme 1) utilizing Pd-catalyzed aminocarbonylation as a key reaction.

Because of its diverse utility and efficiency, Pd-catalyzed carbonylation process is regarded as most useful catalytic process for the direct amide bond formation from the standpoint of industrial application.[3] In case of the *N*H-containing amide substrate **2**, we have already investigated typical hydroxycarbonylation reaction, which afforded the desired acid **3** in high yields.[4] Based on this research, we were interested in the direct aminocarbonylation of the aryl bromide **2** with benzazepinone derivative **4** (Scheme 1).

In our previous research, we were interested in the utilization of some inorganic salts as beneficial additive for hydroxycarbonylation, and revealed some rate-accelerating effect of cesium (Cs) salt.[4] As an extension of these tactics, further investigations on the effective base and additives for direct aminocarbonylation were surveyed first. Since nucleophilicity of the benzazepinone *N*H (in **4**) is not high, we paid attention to organic base addi-



Scheme 1. Our tactics.

tive from our preliminary search, as well as other related reports on carbonylation reactions.[5,6] As a first attempt at hydroxycarbonylation reaction (**2** to **3**), we added 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) under standard Heck carbonylation conditions: [$Pd(OAc)_2$-PPh_3 in solvent].[3] These conditions offered a facile hydroxycarbonylation reaction within 3 h heating at around 90–120 °C in the presence of some Cs salt and H_2O (Scheme 2).

Keywords: Vasopressin; Palladium; Carbonylation; Cesium salt; DBU.
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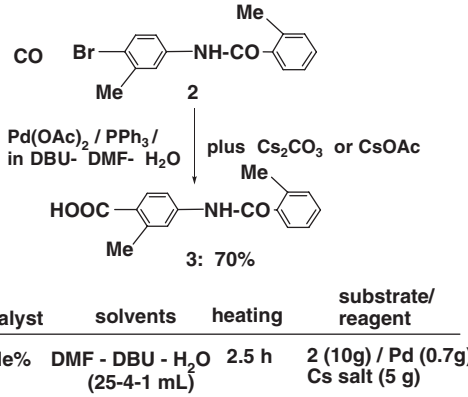
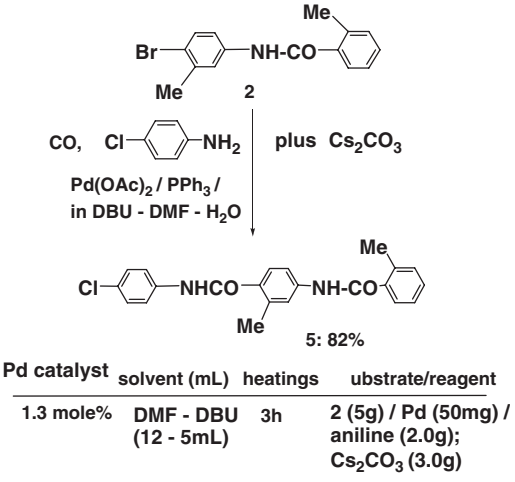


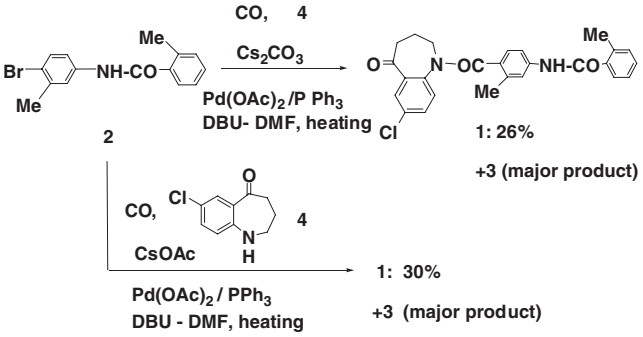
Scheme 2. Hydroxycarbonylation with DBU/cesium salt.

As shown in Scheme 2, effect of the Cs salts (Cs_2CO_3 and CsOAc) was well manifested at higher temperature in the presence of DBU. Without Cs salts, hydroxycarbonylation reaction (with DBU) took much longer time for 60% conversion and increasing amount of arene by-product (Ar-H; about 15% yield) was observed. As a general tendency, DBU preferred Cs_2CO_3 for fast conversion in this hydroxycarbonylation, while Bu_3N preferred the co-existence of CsOAc.[4] Other amines such as 1,5-diaza-bicyclo[4,3,0]-5-nonene (DBN), diisopropylethyamine (DIPEA), 1,4-diazabicyclo[2,2,2]octane (DABCO) were also equally effective for this conversion.[6]

In the next stage, we surveyed on the intermolecular aminocarbonylation reaction with *p*-chloroaniline and aryl bromide **2** as a model study (Scheme 3). Addition of Cs_2CO_3 (ca 1 equiv) and DBU was proven to be beneficial for the faster reaction. Conventional conditions usually took ca. 10 h to complete this conversion (without pressure). While the reaction was getting faster (black mixture) with increasing amount of DBU (1–3 weight to **2**), the isolation of crude product was most easily carried out with 1 weight of DBU to **2**, affording the desired amide product in 82% yield (although unoptimized).



Scheme 3. Aminocarbonylation with DBU/cesium salt.



Scheme 4. Aminocarbonylation with benzazepinone-1.

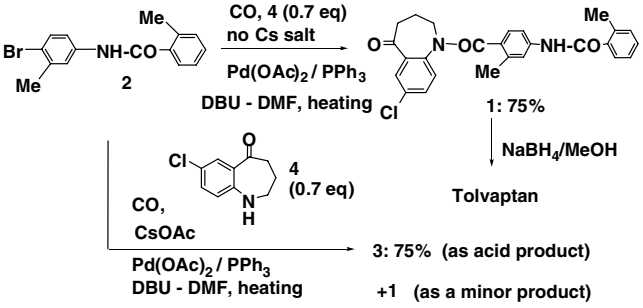
We next investigated the aminocarbonylation reaction to tolvapatan intermediate **1**. Since the nucleophilicity of the benzazepinone **4** is not high, we first attempted the aminocarbonylation in the presence of both Cs salts and DBU (Scheme 4).

Contrary to the previous study (Scheme 3), aminocarbonylation with benzazepinone (**4**; using equivalent or excess to **2**) in the presence of Cs salts and DBU gave unsatisfactory results (low yield and mixture of products). Instead, the hydroxycarbonylation to afford undesired acid **3** prevailed as a major reaction path, which indicated that Cs salts strongly accelerated the hydroxycarbonylation reaction with less reactive benzazepinone **4**.

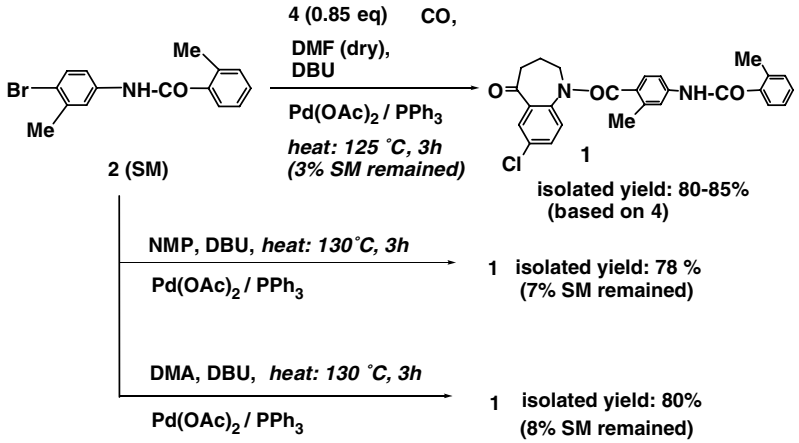
To prevent undesired hydroxycarbonylation, water should be removed from the reaction media (including apparatus for carbonylation). Eventually, the problem could be alleviated by simply conducting the reaction with DBU in *N*,*N*-dimethylformamide (DMF) in anhydrous conditions, without any Cs salts present in the reaction mixture as shown in Scheme 5.

A successful transformation of **1** to tolvaptan was also carried out as shown in Scheme 5 (reduction of **1** and simple isolation: 85% from **1**).

Final optimization was then carried out using different kinds of amide solvents (Scheme 6). We then conducted the reaction in a concentrated mixture with slightly less equivalent (0.85 equiv) benzazepinone **4** under tightly



Scheme 5. Aminocarbonylation with benzazepinone-2.



Scheme 6. Aminocarbonylation with benzazepinone-3.

anhydrous conditions. Conversion of the aryl bromide **2** was most effectively attained in DMF, while almost same conversion was feasible with *N*-methylpyrrolidone (NMP) and *N,N*-dimethylacetamide (DMA) (3 h at 130 °C).

We also attempted the blank experiment without benzazepinone **4**, which revealed the formation of small amount of acid **3** and dimethylamide (by-product from dimethylamine contained in DMF).

From the results obtained and shown in the Schemes, we tentatively concluded that DMF was a preferable (convenient) solvent for this aminocarbonylation, although small amounts of by-products were present in the mixture with trace amount of bromide unchanged. It is interesting to note that carbonylation was slightly faster in DMF than in NMP and DMA, and background reaction (as observed in blank experiment) indicated the decomposition of DMF during reaction under basic conditions. Decomposition of DMF under Pd-catalyzed amination was reported and thus DMF could work as a CO source in this case.[7]

In summary, we have attained an efficient aminocarbonylation to the tolvaptan intermediate **1** in a single step in reproducible yield. This is the notable example of aminocarbonylation reaction, in which less reactive benzazepinone **4** has been employed for the first time as a reaction partner.[8]

Further improvement will be possible using other CO source.[9,10] Progress toward these convenient and safe carbonylation processes is under active investigation in our laboratories for the production of tolvaptan and other drug candidates.[2,11]

Acknowledgments

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8. *Experimental procedure*: Substrates were well-dried and placed in the reaction flask, while exchanging with Ar with stirring before dissolving in the dried solvents (DMF etc.). Thus, under tightly anhydrous conditions, a stirred suspension of aryl bromide (**2**, 3.2 g) and benzazepinone (**4**, 1.8 g) in DMF (6 mL)-DBU(2.5 mL) was charged with CO at room temperature, before the quick addition of Ph_3P (8 mol%) and $Pd(OAc)_2$ (1.3 mol%) to the mixture. Resulting mixture was then gradually heated at around 125 °C for ca. 3 h. Constant gas absorption was observed, while the mixture was maintained as orange colored suspension. (In the case of DMF and NMP, a dark mixture formed at this stage.) HPLC analysis (UV) at 3 h indicated ca. 3 area % of SM remained along with the product level reached to ca. 60 area %. After cooling to room temperature, CO was removed from the reaction flask by the aid of Ar bubbling. The mixture was then diluted with AcOEt (150 mL)–NaOH aq (0.5 N, 50 mL) with stirring. Aqueous layer was separated and organic layer was washed well with dil HCl to remove DBU and other polar materials. Crude extracts were further washed with brine and neutral organic products were dried over $MgSO_4$. Concentration of the dried solvents gave the crude residue, which was purified by SiO_2 column chromatography to afford the desired amide product (81–85%) with 99.1% purity as judged by HPLC.

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11. Our preliminary survey has indicated that attempted carbonylation of **2** with various metal carbonyl derivatives according to Ref. 9 and 10 gave rather unsatisfactory results (product yields were mostly less than 40%). We also observed that hydroxycarbonylation was faster (prevailed) with reported metal carbonyl derivatives rather than aminocarbonylation (under normal heating conditions).