Palladium-Catalyzed Synthesis of 1,2,3,4-Tetrahydro-5*H*-2-benzazepin-5-ones

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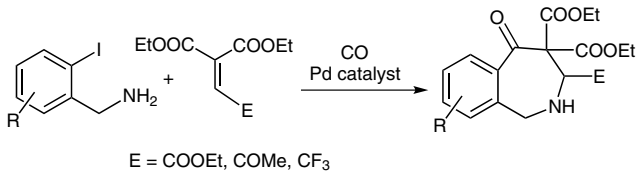
Abstract: Palladium-catalyzed intermolecular cyclocarbonylation of 2-iodobenzylamines with Michael acceptors produces 1,2,3,4-tetrahydro-5*H*-2-benzazepin-5-one derivatives in moderate to good yields. This methodology enables the direct preparation of highly functionalized 1,2,3,4-tetrahydro-5*H*-2-benzazepin-5-ones from readily available starting materials.

Key words: cyclocarbonylation, heterocycles, palladium, 1,2,3,4-tetrahydrobenzazepin-5-one, Michael acceptor

Some 1,2,3,4-tetrahydro-5*H*-2-benzazepin-5-one derivatives have received attention due to their biological activities.[1] They can also serve as synthetic intermediates for dual inhibitors of acetylcholinesterases and serotonin transporters[2] as well as inhibitors for the re-uptake of norephedrine, dopamine, and serotonin.[3] However, little is known about their synthesis, in particular, by means of direct preparation from readily available starting materials. Most common syntheses rely on the intramolecular Friedel–Crafts acylation of *N*-benzyl-β-aminoacids or their acid chlorides using $AlCl_3$ or polyphosphoric acid (PPA).[3,4] Another example includes oxidation of the corresponding alcohols derived from the hydroboration of 1,3-dihydrobenzazepines.[2]

We have recently demonstrated the palladium-catalyzed intermolecular cyclocarbonylation of 2-iodoanilines and diethyl ethoxycarbonylbut-2-en-1,4-dioate affording 2,3,3-triethoxycarbonyl-2,3-dihydro-4(1*H*)-quinolinone in moderate to good yields.[5] These results encouraged us to extend the study on the cyclocarbonylation to the reaction of 2-iodobenzylamines with Michael acceptors including diethyl ethoxycarbonylbut-2-en-1,4-dioate. We now wish to report that this method offers a facile approach toward highly functionalized 1,2,3,4-tetrahydro-5*H*-2-benzazepin-5-ones (Scheme 1).

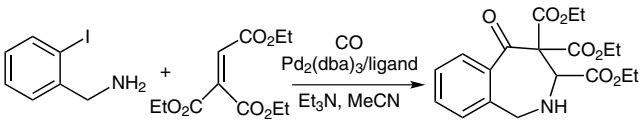


Scheme 1

When 2-iodobenzylamine (**1a**) was treated with diethyl ethoxycarbonylbut-2-en-1,4-dioate (**2a**) under the optimal conditions for the carbonylation of 2-iodoaniline with **2a**,[5,6] 3,4,4-triethoxycarbonyl-1,2,3,4-tetrahydro-5*H*-2-benzazepin-5-one (**3aa**) was isolated in 77% yield (Table 1, entry 1). It should be noted that no γ-benzolactam was formed, which would result from intramolecular cyclocarbonylation of **1a**. Although the nature of the phosphane ligands in this reaction seems not to be crucial compared to the reactions of 2-iodoanilines,[5] PCy_3 (as HBF_4 salt)[7] is the best ligand among the phosphanes examined. The reaction took place to give **3aa** in excellent isolated yield even under 100 psi of carbon monoxide (entry 5), whereas use of a reduced amount of Et_3N caused significant decrease in the yield (entry 6).

Having established the optimized conditions, a range of benzylamines with different substituent patterns were treated with **2a** (Figure 1 and Table 2). The corresponding 1,2,3,4-tetrahydro-5*H*-2-benzazepin-5-ones **3** were isolated in moderate to excellent yields (entries 1–6). Note that substrates having substituents at the *ortho* position of the aminomethyl or iodo group also afforded the expected products in reasonable yields (entries 4–6).

Table 1 Screening for the Intermolecular Cyclocarbonylation of **1a** and **2a**[a]



1a **2a** **3aa**

Entry	Ligand	Amount of Et_3N (equiv)	CO (psi)	Yield (%)[b] of **3aa**
1	ArP(*t*-Bu)$_2$[c]	10.0	500	77
2	PPh_3	10.0	500	73
3	P(*t*-Bu)$_3$HBF$_4$	10.0	500	85
4	PCy_3HBF_4	10.0	500	87
5	PCy_3HBF_4	10.0	100	89
6	PCy_3HBF_4	5.0	100	68

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.2 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (0.025 mmol), ligand (0.1 mmol), Et_3N (10 mmol or 5 mmol), MeCN (2 mL), 80 °C, 20 h.
[b] Isolated yield after column chromatography.
[c] 2-(Di-*tert*-butylphosphino)biphenyl.

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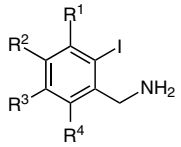
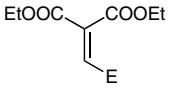


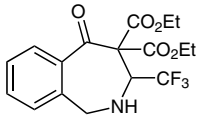
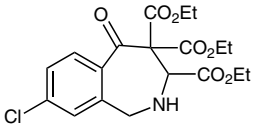
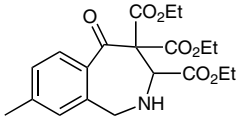
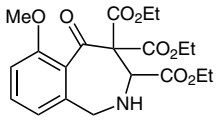
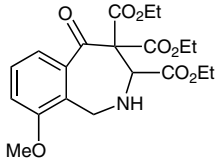
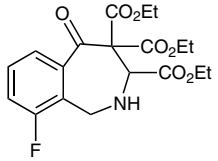
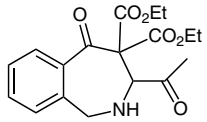
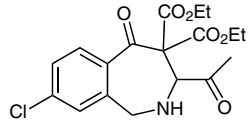
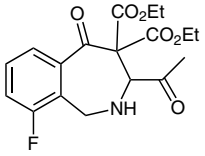
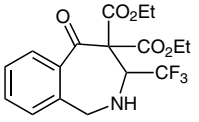
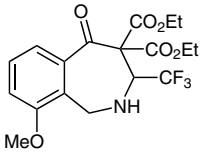
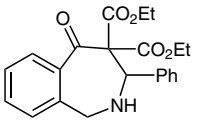
1a: $R^1 = R^2 = R^3 = R^4 = H$
1b: $R^1 = R^3 = R^4 = H$, $R^2 = Cl$
1c: $R^1 = R^2 = R^4 = H$, $R^3 = Cl$
1d: $R^1 = R^2 = R^4 = H$, $R^3 = Me$
1e: $R^1 = OMe$, $R^2 = R^3 = R^4 = H$
1f: $R^1 = R^2 = R^3 = H$, $R^4 = OMe$
1g: $R^1 = R^2 = R^3 = H$, $R^4 = F$



2a: E = COOEt
2b: E = Ac
2c: E = CF_3
2d: E = Ph

Figure 1 The starting materials

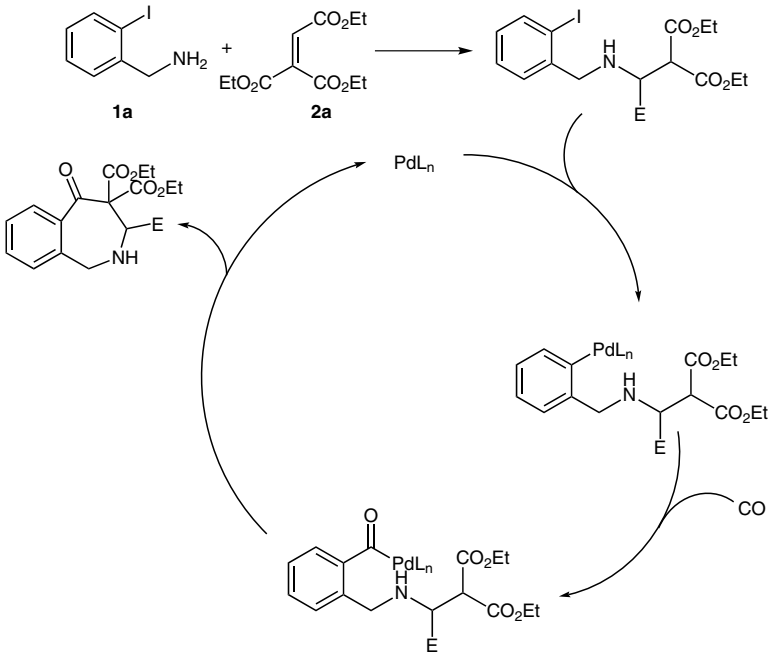
Table 2 Synthesis of 1,2,3,4-Tetrahydro-5*H*-2-benzazepin-5-one[a]

Entry	1	2	Product	Yield (%)[b]
1	**b**	**a**	 **3ba**	80
2	**c**	**a**	 **3ca**	93
3	**d**	**a**	 **3da**	83
4	**e**	**a**	 **3ea**	62
5	**f**	**a**	 **3fa**	69
6	**g**	**a**	 **3ga**	74
7	**a**	**b**	 **3ab**	43 (51)
8	**c**	**b**	 **3cb**	(52)
9	**g**	**b**	 **3gb**	(47)
10	**a**	**c**	 **3ac**	44 (54)
11	**f**	**c**	 **3fc**	(64)
12	**a**	**d**	 **3ad**	16[c]

[a] Reaction conditions were the same as in Table [1], entry 5.
[b] Isolated yield. The values in parentheses are the reaction yields using 2.0 mmol of **2**.
[c] Reaction was performed at 100 °C.

Other Michael acceptors were also examined. When ethyl 2-ethoxycarbonyl-4-oxo-2-pentenoate (**2b**) was treated with **1a**, 3-acetyl-4,4-diethoxycarbonyl-1,2,3,4-tetrahydro-5*H*-2-benzazepin-5-one (**3ab**) was formed in 43% yield (entry 7). Use of an increased amount of **2b** to two equivalents, based on **1a**, improved the product yields to 51%. Similarly, the corresponding products, **3cb** and **3gb** were isolated from the reaction of **1c** and **1g** with **2b**, respectively (entries 8 and 9). Ethyl 2-ethoxycarbonyl-3-trifluoromethylpropenoate (**2c**) was also successfully used as a carbonylation partner, with the corresponding benzazepin-5-ones being isolated in 54–64% yield when two equivalents were used. These results are in sharp contrast with those of 2-iodoanilines, where **2b** and **2c** were not successfully used.[5] When diethyl benzylidenemalonate (**2d**) was used as a Michael acceptor, the reaction proceeded to some extent at 100 °C, but the yield of the expected product **3ad** was unsatisfactory (entry 12). In this olefin, increasing temperature to 120 °C did not improve the yield (9%).

A possible reaction mechanism for the formation of **3** consists of the following steps (Scheme 2):[5] (1) aza-Michael



Scheme 2 A possible reaction mechanism

addition of **1** to **2** to form the Michael adduct, (2) oxidative addition of Pd(0) to the C–I bond of the adduct,[8] (3) insertion of carbon monoxide into the Pd–C bond to form aroylpalladium species, and (4) nucleophilic attack of the internal malonate anion on the aroylpalladium intermediate to give the product **3** and regeneration of Pd(0) species.[9] One of the crucial steps for the successful reaction is the initial aza-Michael addition. The higher nucleophilic reactivity of the aminomethyl group (i.e., **1**) compared to the anilino group (i.e., 2-iodoanilines),[5] may allow the use of a wider range of Michael acceptors (i.e., **2a**–**c**).

In conclusion, we have demonstrated an effective synthetic process for the preparation of 1,2,3,4-tetrahydro-5*H*-2-benzazepin-5-ones by palladium-catalyzed intermolecular cyclocarbonylation of 2-iodobenzylamines and Michael acceptors. This methodology enables the direct preparation of highly functionalized 1,2,3,4-tetrahydro-5*H*-2-benzazepin-5-ones.

Acknowledgment

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(6) **General Procedure**: A mixture of **1** (1.0 mmol), Michael acceptor **2** (1.2 mmol or 2.0 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (0.025 mmol, 25.9 mg), PCy_3HBF_4 (0.1 mmol, 36.8 mg), and Et_3N (10 mmol, 1.01 g) in MeCN (2 mL) was charged in a glass liner, equipped with a magnetic stirring bar. The glass liner was then inserted into a 45-mL autoclave. The autoclave was flushed with CO (5 ×) and pressurized to 100 psi. The autoclave was heated at 80 °C with stirring. After the reaction, the autoclave was cooled to r.t. prior to the release of CO. The solvent was evaporated under reduced pressure, and the product was purified by silica gel column chromatography with *n*-hexane and Et_2O as the eluent.
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