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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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Concise Palladium-Catalyzed Synthesis of Dibenzodiazepines and Structural Analogues

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Supporting Information

ABSTRACT: A general and highly efficient protocol for the synthesis of dibenzodiazepines and their structural analogues is reported. In the presence of catalytic quantities of palladium, readily accessible precursors are cross-coupled with ammonia and then spontaneously undergo an intramolecular condensation to form the corresponding dibenzodiazepines in one step. This new strategy is applicable to the construction of a wide variety of dibenzooxazepines and other structurally related heterocycles.

Pharmacologically active dibenzodiazepines and their structural analogues, dibenzooxazepines and dibenzo(di/ox)azepinones,[1,2] account for a significant portion of widely prescribed azepine-based drugs. Unfortunately, access to a large number of structural derivatives of these heterocycles is hindered by their multistep syntheses. Since the first reported synthesis of dibenzodiazepine derivatives by Schmutz in 1964−67 (clozapine and loxapine; Figure 1), limited progress has been made.[3] Existing routes to dibenzodiazepines (and their derivatives) generally rely on the preparation of amide[4] or lactam[5] intermediates and subsequent functionalization of the heterocyclic scaffold to introduce additional substituents (Scheme 1). Such transformations typically require harsh conditions, purification after each synthetic step, and the use of protecting groups.[1b,c,5c,6] Most previously reported synthetic pathways require reduction of a NO_2 group and have limited functional group compatibility, whereas coupling of substrates with two free NH_2 groups leads to a mixture of products. Thus, there is a need for an efficient, concise, and general protocol to provide access to a diverse range of dibenzodiazepine derivatives.

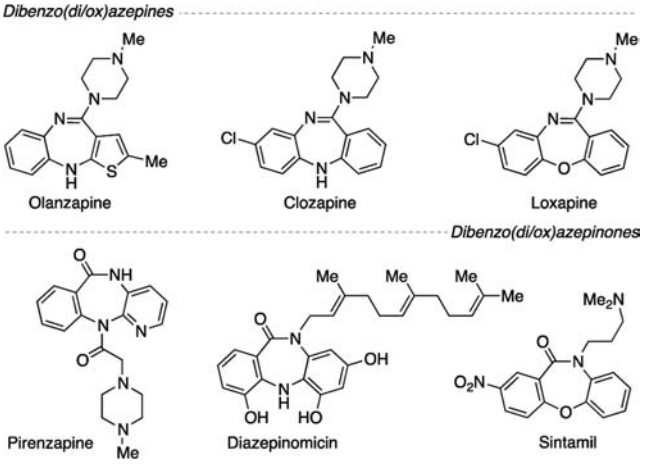
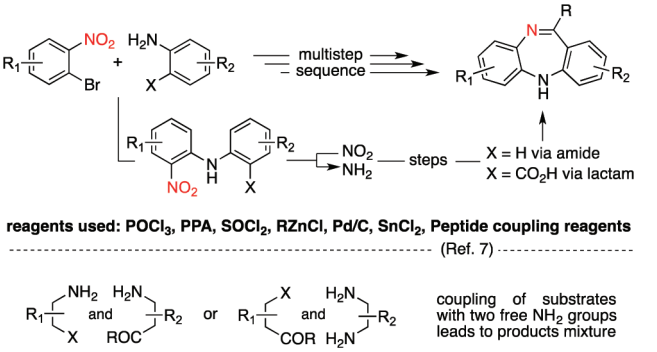
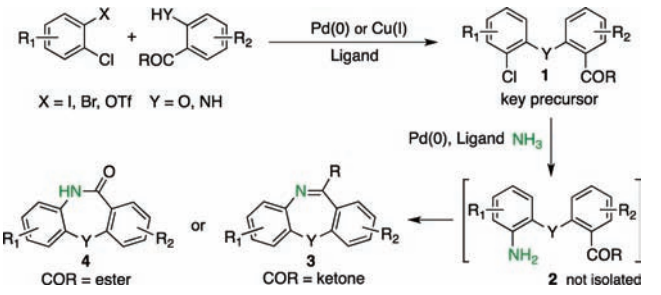


Figure 1. Pharmacologically active dibenzodiazepine derivatives.

Scheme 1. Pairs of Coupling Partners Traditionally Used for Synthesis of Dibenzodiazepines



Scheme 2. Proposed Synthesis of Dibenzo(di/ox)azepines and Dibenzo(di/ox)azepinones

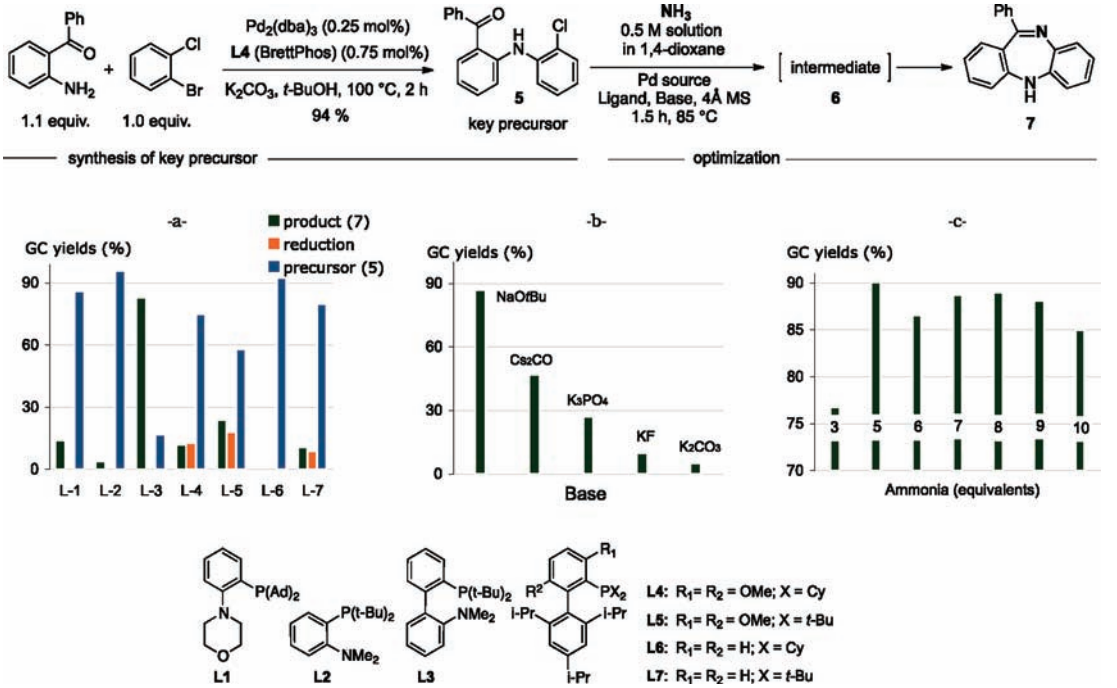


Herein we report a versatile method for the synthesis of dibenzodiazepine analogues via the formation of key precursor **1**, which is readily accessed by cross-coupling of *o*-carbonyl(anilines or phenols) with 1,2-dihaloarenes (or their equivalents) (Scheme 2).[7] This synthetic strategy is based on the notion that in the presence of catalytic quantities of palladium, this precursor would generate intermediate **2** via cross-coupling with ammonia[8] and further spontaneously undergo an intramolecular condensation to form the corresponding dibenzodiazepine **3** in one step (Scheme 2). We also felt that this new strategy might be applicable to the construction of dibenzooxazepines (**3**; Y = O) or other structural analogues, such as dibenzodiazepinones (**4**; Y = NH) and dibenzooxazepinones (**4**; Y = O). To our knowledge, these constitute the first application of the Pd-catalyzed coupling of ammonia in the synthesis of complex heterocycles.[8]

Received: July 5, 2011
Published: August 12, 2011

dx.doi.org/10.1021/ja206229y | J. Am. Chem. Soc. 2011, 133, 14228–14231

Scheme 3. Optimization Study for the Synthesis of Dibenzodiazepines

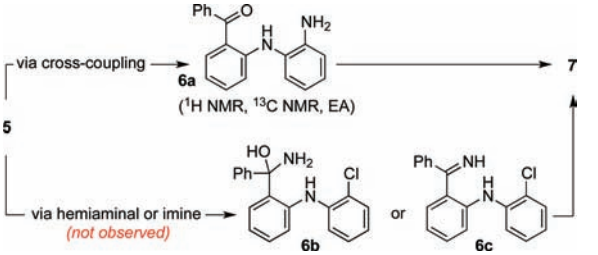


In order to test our hypothesis, aniline **5**, which was prepared in 94% yield via a C−N coupling reaction[7] of 2-aminobenzophenone and 2-bromochlorobenzene, was selected as the diarylamine precursor (Scheme 3). Initial studies were carried out on a 0.5 mmol scale at temperatures ranging from 80 to 110 °C using a variety of palladium sources, bases, and phosphines.[7a,8c] We found that an efficient catalyst for the desired transformation could be formed from the combination of *t*-BuDavePhos (**L3**), $Pd_2(dba)_3$, and NaO*t*-Bu at 85 °C. Other combinations of catalyst, ligand, and base (Scheme 3a,b) led to the reduction of starting precursor **5** or gave low yields of the desired dibenzodiazepine **7**. The use of 1,4-dioxane as the solvent provided the optimal yield of product and allowed for a convenient protocol to be developed in which a commercially available solution of ammonia (0.5 M in 1,4-dioxane) could be used as the source of NH_2.[8a] The optimal range of equivalents of ammonia was broad (5−10 equiv; Scheme 3c), which simplifies the experimental operation. The highest conversion was achieved when 5 equiv of NH_3 was employed at a 0.1 M concentration of precursor.

In principle, the reaction of precursor **5** with ammonia could produce three possible reactive intermediates, **6a**−**c** (Scheme 4), that could give rise to dibenzodiazepine **7**. In order to differentiate among these, the reaction was carried out under the standard conditions but in the absence of molecular sieves. Compound **6a** was then isolated as the only observable intermediate, and the structure was assigned on the basis of its ^1H and ^{13}C NMR spectra and the results of elemental analysis. No evidence for the presence of either a hemiaminal or an imine was detected. It should be also noted that no diarylated product[8] was formed under the optimized conditions. Presumably, the intramolecular condensation of intermediate **6a** yields **7** faster than an additional intermolecular Pd-mediated cross-coupling with **5** can occur.

We next prepared a range of diarylamine precursors **8** that were subjected to our optimized conditions to provide a range of

Scheme 4. Plausible Pathways for the Formation of Dibenzodiazepine



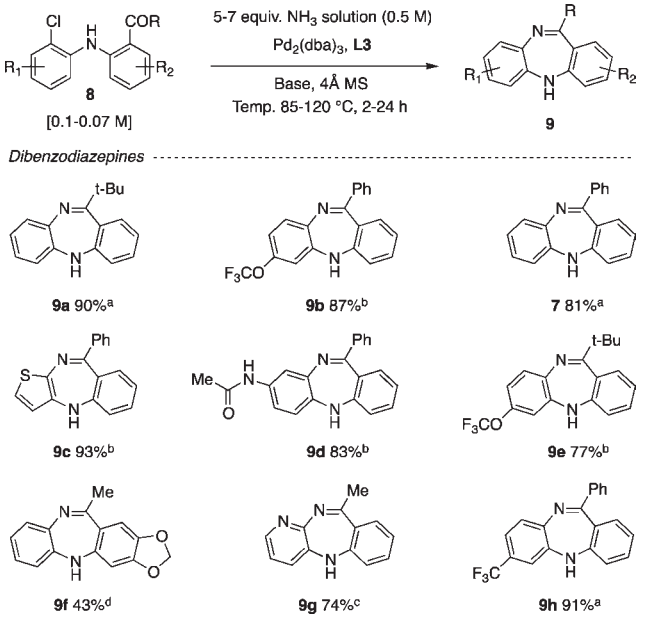
dibenzodiazepine derivatives in good to excellent yields (Table 1). Notably, both electron-rich and electron-deficient diarylamine precursors were transformed efficiently. Under these conditions, heterocycles such as diaxoles, thiols, and pyridines as well as various functional groups were tolerated. Interestingly, our optimized conditions failed to provide the desired dibenzodiazepine products in the case of acetophenone-core precursors (R = Me). However, we found that when the amount of ammonia was increased to 7 equiv, the catalyst loading to 4 mol %, and the temperature to 120 °C, the desired transformation proceeded readily in the presence of Cs_2CO_3, albeit in lower yields (products **9f** and **9g**; Table 1).

With suitable access to dibenzodiazepines in hand, we next examined the scope of the reaction to form dibenzooxazepines. For this transformation, the key diarylether precursors **12** were prepared via copper-catalyzed C−O cross-coupling reactions of commercially available 2-carbonylphenols **10** and 1,2-dihaloarenes **11** (Table 2).[7d] As expected, in the presence of $Pd_2(dba)_3$, **L3**, and base (NaO*t*-Bu or Cs_2CO_3), reactions of such precursors (both electron-rich and electron-deficient) with ammonia afforded the dibenzooxazepines as single products in good yields (Table 2).

As an expansion of this study, we next explored the preparation of structurally related dibenzodiazepinones and

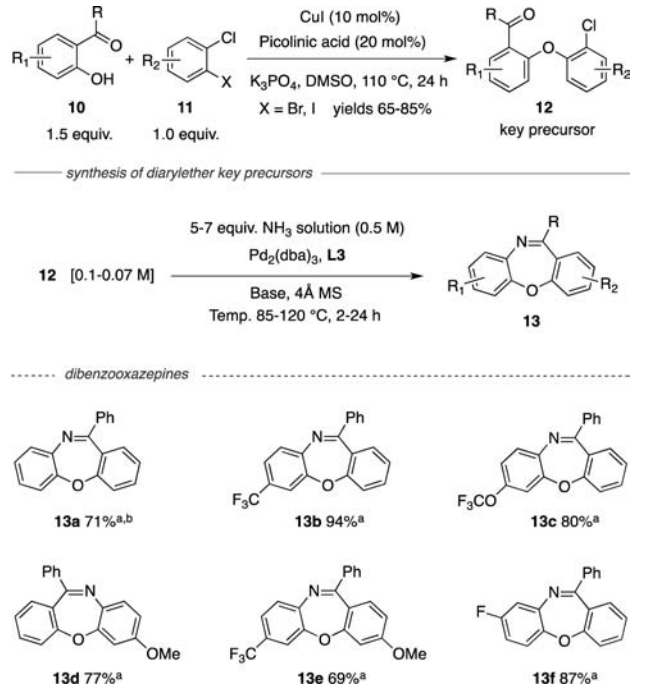
dx.doi.org/10.1021/ja206229y |*J. Am. Chem. Soc.* 2011, 133, 14228–14231

Table 1. Palladium-Catalyzed Synthesis of Dibenzodiazepines



Conditions (yields are averages of two runs): [a] Precursor (1.0 mmol), 0.5 M ammonia solution in 1,4-dioxane (10 mL, 5.0 mmol), $Pd_2(dba)_3$ (0.015 mmol), **L3** (0.05 mmol), NaO*t*-Bu (1.5 mmol), 85 °C, 2 h. [b] 5 h. [c] Precursor (1.0 mmol), 0.5 M ammonia solution in 1,4-dioxane (14 mL, 7.0 mmol), $Pd_2(dba)_3$ (0.02 mmol), **L3** (0.06 mmol), Cs_2CO_3 (4.0 mmol), 120 °C, 24 h. [d] See ref 9.

Table 2. Palladium-Catalyzed Synthesis of Dibenzooxazepines



Conditions (yields are averages of two runs): [a] Precursor (1.0 mmol), 0.5 M ammonia solution in 1,4-dioxane (10 mL, 5.0 mmol), $Pd_2(dba)_3$ (0.015 mmol), **L3** (0.05 mmol), NaO*t*-Bu (1.5 mmol), 85 °C, 5 h. [b] The precursor can be prepared from 1,2-dibromobenzene or 1-bromo-2-iodobenzene.

Scheme 5. Formation of Dibenzodiazepinone

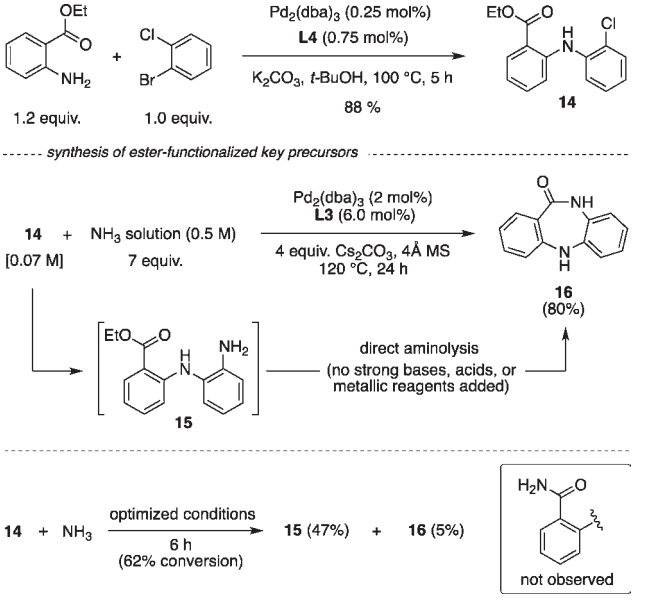
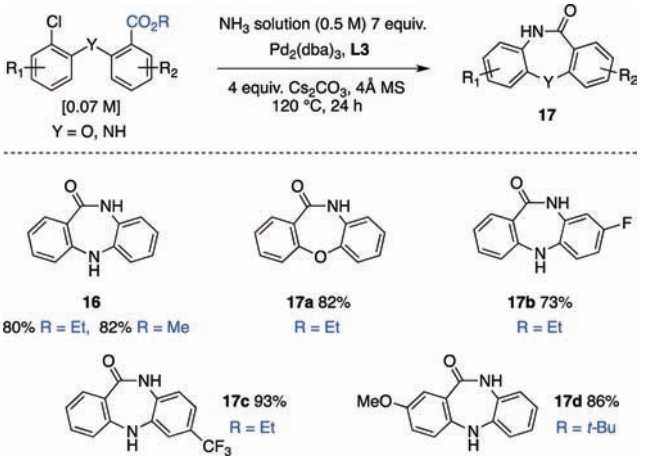


Table 3. Palladium-Catalyzed Synthesis of Dibenzodiazepinones and Dibenzooxazepinones[a]



[a] Conditions (yields are averages of two runs): precursor (1.0 mmol), 0.5 M ammonia solution in 1,4-dioxane (14 mL, 7.0 mmol), $Pd_2(dba)_3$ (0.02 mmol), **L3** (0.06 mmol), Cs_2CO_3 (4.0 mmol), 120 °C, 24 h.

dibenzooxazepinones via a tandem amination−cyclization approach. For this study, commercially available ethyl-2-aminobenzoate and 1-bromo-2-chlorobenzene were chosen as test substrates. Precursor **14** was then prepared via a C−N cross-coupling reaction and isolated in 88% yield (Scheme 5). In order to prevent cleavage of the ester functional group, this precursor was subjected to the ammonia coupling reaction conditions in the presence of Cs_2CO_3 as the base. As a result, dibenzodiazepinone **16** was obtained in 80% yield. On the basis of previous observations, we envisioned that **16** could be generated in a one-pot process via the intramolecular aminolysis of reactive intermediate **15** formed from the cross-coupling of **14** with ammonia (Scheme 5). To determine the nature of the intermediate formed, precursor **14** was allowed to react under the

optimized conditions for 6 h. Consequently, **15** was isolated in 47% yield, while no products other then **16** and precursor **14** were observed. It should be noted that neither strong base, acid, nor metallic reagents were required to promote the cyclization of **15**, representing a first case of direct aminolysis in the presence of a catalytic amount of palladium.[10] Further investigations using several ester-functionalized precursors (prepared in the same way as **14**) were performed. As shown in Table 3, the cascade transformations were successful and quite general, tolerating variation of the substituents of the precursors and leading to the formation of the expected heterocycles in high yields. We were also pleased to find that substrates bearing a wide range of esters, such as *tert*-butyl, ethyl and methyl, which significantly simplifies the synthetic protocol with regards to the choice of available starting material.

In conclusion, we have developed a practical and general protocol for the Pd-catalyzed synthesis of dibenzodiazepines and their structural analogues, an important class of heteroaromatic compounds. This method was applicable to a wide variety of precursors, and good yields of pure heterocycles were obtained. The synthetic advantage of this route is exemplified by the successful preparation of these compounds via the catalytic and shortest sequence reported to date through the use of simple, easily accessible starting materials.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, characterizations, spectral data for all compounds, and complete ref 2a. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

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■ ACKNOWLEDGMENT

This work was supported by an educational donation provided by Amgen and from the National Institutes of Health (Grant GM-58160), to whom we are grateful. We also thank FMC Lithium for a generous gift of ClP(*t*-Bu) and Nippon Chemicals for gifts of chemicals and unrestricted funds. We thank reviewer 3 for thoughtful and constructive comments and suggestions concerning the mechanism of formation of **7**.

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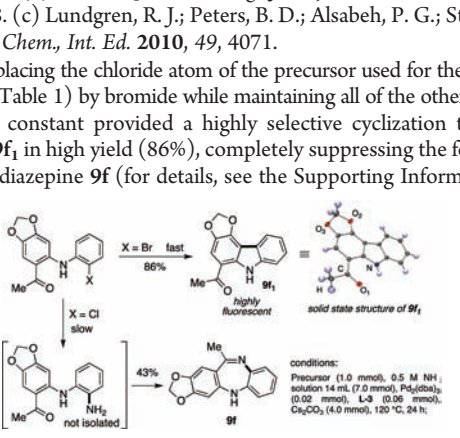
(9) Replacing the chloride atom of the precursor used for the preparation of **9f** (Table 1) by bromide while maintaining all of the other reaction conditions constant provided a highly selective cyclization that gave carbazole $\mathbf{9f_1}$ in high yield (86%), completely suppressing the formation of dibenzodiazepine **9f** (for details, see the Supporting Information).



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