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Palladium-catalyzed [5+2] oxidative annulation of *N*-Arylhydrazones with alkynes through C–H activation to synthesize Benzo[*d*][1,2] diazepines

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ABSTRACT

An efficient and novel method using palladium catalyst for the synthesis of benzo[*d*][1,2]diazepines by [5 + 2] annulation of *N*-arylhydrazones with alkynes has been developed. This methodology undergoes through eight membered palladacycle serving as a backbone for the formation of C–C/C–N bond to provide benzodiazepine derivatives in moderate to good yield.

1. Introduction

In the light of history *N*-Heterocyclic compounds have emerged as an important motif to construct wide range of reactive intermediates, drugs, and bioactive molecules.[1a-c] Particularly, benzodiazepines have been recognized as versatile scaffold due to their promising biological and pharmacological activities.[2a-e] These moieties are found to be important tools in drug discovery as well as they are potent antitumor,[3a-d] anti-HIV,[4a,b] anti inflammatory[5a,b] and central nervous system (CNS) agents[6] (Fig. 1). Moreover, 1,2-diazapine analogs are important scaffolds in organic synthesis as it provides the pathway to synthesize other cyclic compounds.[7]

Over the past decades the synthetic community have witnessed the application of hydrazone in organic synthesis to synthesize plethora of compounds.[8a-e] More conveniently they have been emanated as powerful synthons for constructing diverge range of cyclic compounds through transition metal catalyzed or transition metal free reactions. Some of the reaction of hydrazone includes [3 + 2] cycloaddition with aryne or alkyne,[9a-c] intramolecular cycloaddition with internal olefins,[10a,b] transition metal catalyzed intra- and inter-molecular annulation[11a-d] etc. Being an effective precursor for the establishment of five and six membered *N*-heterocyclic compounds the ease of constructing higher member ring still remain unexplored.[12a,b]

Metal catalyzed annulation involving C–H activation as a key step has gained lot of interest among researchers all over the world as it provide the elegant protocol to construct diverse range of cyclic compounds as it overshadows the traditional pattern which requires prefunctionalized substrate.[13a-i] The other credential to this strategy is that it offers the shortest possible route, improve atom economy of organic synthesis.[14a-c]

In context to this metal catalyzed C–H activation proves to be an efficient protocol in [3 + 2] or [4 + 2] cycloaddition reaction to build up cyclic scaffolds which are difficult to synthesize by conventional method.[15a-e] However, very few reports has been documented of [5 + 2] cycloaddition to construct seven membered ring motif employing palladium catalyst. [5 + 2] oxidative annulation of *o*-arylanilines with alkynes to synthesize imine-containing dibenzo[*b*,*d*]azepines with high stereoselectivity through Pd(II) was disclosed by Luan and co-workers[16] (Scheme 1A). Recently, Thikekar et al. described regioselective synthesis of 1,2-fused-indole diazepines through [5 + 2] annulation of *o*-indolo anilines with alkynes employing palladium catalyst[17] (Scheme 1B). Leading from these examples and our continuing interest in transition metal

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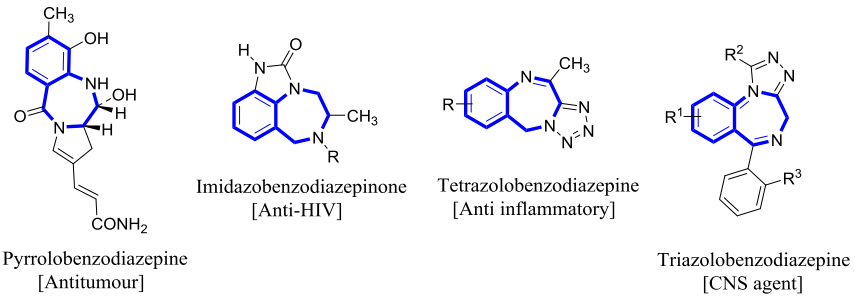
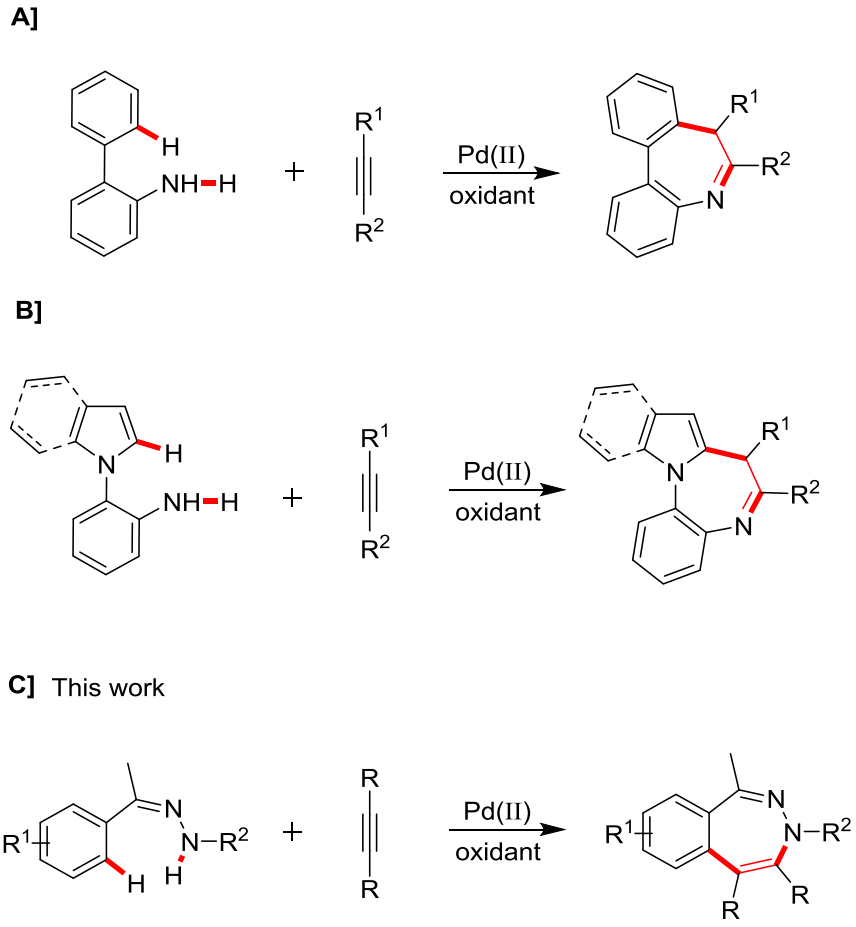


Fig. 1. Potent biologically active Benzodiazepine core.



Scheme 1. Pd(II) catalyzed [5 + 2] annulation of alkynes.

catalyzed C–H activation[18a-f] herein we report the first Pd(II) catalyzed [5 + 2] annulations of *N*-arylhydrazones with alkyne to synthesize benzo[*d*][1,2]diazepines through C–H activation under mild condition (Scheme 1C). To the best of our knowledge, no previous synthesis of benzo[*d*][1,2]diazepines have been reported in the literature.

2. Results and discussion

In order to obtain optimized reaction condition *N*-phenylhydrazone **1a** was treated with diphenyl acetylene **2a** in the presence of Pd(II) catalyst and Cu(II) as oxidant (Table 1). It was noted that no desired transformation was observed on employing Ru(II) catalyst under different solvent system (Table 1, entries 1–3). However, switching over to $PdCl_2$ catalyst afforded the product **3a** in 22% yield in THF and slight increased in yield was recorded when solvent system was changed to 1,4-dioxane (Table 1, entries 4–5). Furthermore, investigation revealed that replacement of $PdCl_2$ with $Pd(OAc)_2$ and using 1,4-dioxane as solvent gave remarkable yield turning out to be optimized condition for the reaction: $Pd(OAc)_2$ catalyst (10 mol %), $Cu(OAc)_2$ oxidant (1 equiv.), at 100 °C in 1,4-dioxane for 12 h (Table 1, entry 6). Changing the solvent or altering the reaction temperature doesn't increase the yield (Table 1, entries 7–11). Moreover, reasonable yield of the expected product was obtained when $CuCl_2$ or dioxygen were used as oxidant and no yield was obtained when the reaction was carried out without catalyst (Table 1, entry 12–14).

With the optimized condition in hand for unusual [5 + 2] annulation, the substrate scope of the reaction was explored by employing broad range of hydrazone (**1a-1l**) to react with