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Synthesis of 1,4-benzodiazepinones via palladium-catalysed allene carbopalladation/amination domino sequence

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ABSTRACT

Vinyl-substituted 1,4-benzodiazepinones were obtained in good yields (10 examples, 61–82% yield) via the reaction between *N*-allenyl anthranyl amides and aryl iodides under Pd(0) catalysis. This new single cycle catalytic domino transformation involves a C–C followed by an N–C bond formation.

1. Introduction

Since the discovery of chlordiazepoxide, by L. Sternbach, in the mid fifties, 1,4-benzodiazepines became one of the most popular heterocyclic structures in the history of drugs [1]. The benzodiazepine motif, found incorporated into a number of pharma molecules such as CNS drugs [2], antibiotics [3], antithrombotics [4], anti-HIV drugs [5], as well as peptidomimetics [6] is nowadays considered as a privileged structure [7].

In particular, the sub-set of 1,4-benzodiazepin-5-ones occupies an important role in medicinal chemistry [8]. For example, tri- as well as tetra-cyclic systems containing the 1,4-diazepin-5-one motif proved to be useful candidates for a wide array of therapeutic applications [9,10]. The antihistaminic property of tarpane [11], the antibiotic activity of abbeymycin [12], the anti-anxiety effect of flumazenil [13] and the anti-neurodegenerative activity of bretazenil [14] represent remarkable examples (Fig. 1).

Appropriate structural modifications of the above structures may lead to new analogues endowed with interesting biological activities. Accordingly, the search for novel synthetic approaches toward such heterocyclic structures is highly desirable.

Most of the reported methods to prepare 1,4-benzodiazepin-5-ones start from the readily available isatoic anhydride [15]. Although useful solid supported variants of this approach have been reported [16], these methods either require harsh pre-functionalisation conditions, or are not atom economical.

In the context of our ongoing research directed toward the synthesis of heterocycles via transition metal-catalysis, we recently directed our interest toward allenes [17]. These previous studies led us to envision *N*-allenyl anthranyl amides as suitable substrates for the synthesis of α-styryl-substituted 1,4-benzodiazepin-5-ones via a pure domino [18] Pd(0)-catalysed carbopalladation/allylic amination process. This plan proved successful and the present article describes details about this new strategy that widens the existing palladium-based approaches toward 1,4-benzodiazepin-5-ones (Scheme 1) [19].

2. Results and discussion

The required *N*-allenylamide cyclization precursor **1a** was first prepared by DCC promoted condensation between *N*-benzyl-(4-methylpenta-2,3-dienyl)-amine [17f] and *N*-tosyl anthranilic acid [20] under standard conditions (Scheme 2) [21].

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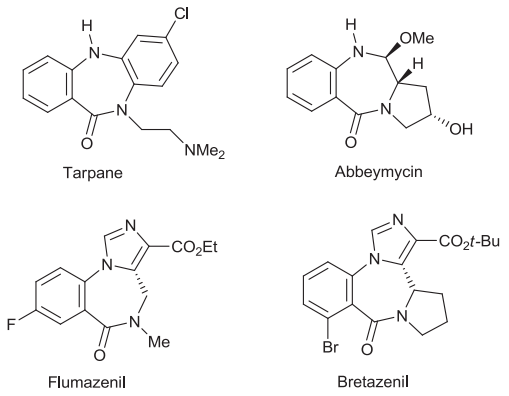
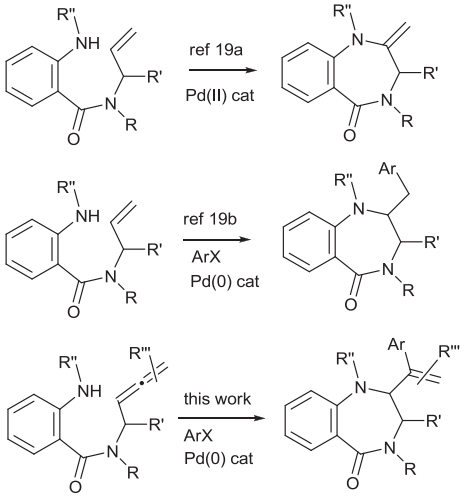


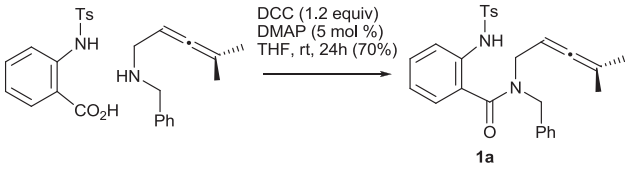
Fig. 1. Some examples of pharmacologically active polycyclic 1,4-benzodiazepinones.

Coupling between **1a** and 4-iodotoluene (1.2 equivalents) to give the benzodiazepine **2a** was chosen as model reaction to investigate the planned carbopalladation/amination sequence (Table 1).

First, we investigated the feasibility of the reaction employing phosphine-free conditions. This protocol was recently reported by some of us for the synthesis of γ-lactams via carbopalladation/allylation of allenyl substrates [22,17a]. Accordingly, the catalytically active palladium species was generated by the addition of BuLi (10 mol%) to a solution of $Pd(CH_3CN)_2Cl_2$ (5 mol%) in DMSO. Then, 4-iodotoluene (1.2 equiv.), tetrabutylammonium bromide (TBAB) (20 mol%) and a DMSO solution of the sodium amidate were added in sequence (Entry 1). Although the conversion of the substrate was satisfactory, the expected benzodiazepinone **2a** was isolated in only moderate yields. Switching to $Pd(OAc)_2$/dppf as catalytic system in acetonitrile, decreased dramatically the substrate conversion (Entry 2). We thus decided to come back to the ligandless protocol, optimizing bases and temperatures. The use of Cs_2CO_3 or K_2CO_3 was nearly ineffective either at 50 °C or at 90 °C (Entries 3–5). Conversely, deprotonation of the allenylamide with NaH at 50 °C followed by heating at 90 °C after the addition of the remaining reagents brought about a complete conversion together with a remarkable increase of the yield (Entry 6). Finally, a blank experiment omitting NaH gave no product, thereby confirming the crucial role of that base for the success of the reaction (Entry 7).



Scheme 1. Previously reported Pd-catalysed syntheses of 1,4-benzodiazepin-5-ones and the present approach.



Scheme 2. Generation of the starting cyclization precursor.

With the optimized ligandless conditions in hand, the scope of the domino sequence was next examined on 0.1 mmol scale reactions, reacting **1a** with various aryl iodides (Table 2). Electron-rich 2-, 3- and 4-iodoanisoles reacted smoothly, affording the expected corresponding benzodiazepinones **2b**–**d** in 63%, 63% and 73%, respectively. The reaction of electron poor aryl iodides such as those bearing *para* positioned methoxycarbonyl, nitro, and acetyl functions gave products **2e**–**g** in satisfactory yields (61%, 71% and 68%, respectively). The use of simple iodobenzene led to the expected benzodiazepinone **2h** in 67% yield. The heteroaromatic halide 3-iodopyridine afforded the expected product **2i** in 70% yield. Finally, the same protocol well sustained substitutions on the aromatic ring. Indeed, the *N*-allenyl 3-methyl anthranyl amide **1b** afforded uneventfully benzodiazepinone **2j** (75%) [23].

The formation of 1,4-benzodiazepin-5-ones can be rationalized according to the mechanism depicted in Scheme 3. First, the Pd(0) complex **I** [24] is generated from $Pd(CH_3CN)_2Cl_2$ and *n*-BuLi. After oxidative addition of the iodoarene to **I**, the thus formed PhPdI complex **II** undergoes carbopalladation to give the η^3-allyl complex **IV** via **III**. 7-*Exo* nucleophilic attack by the sodium salt of the sulfonamide (or carbamate) nitrogen atom forms the benzodiazepinone **2a** and regenerates a Pd(0)-species, thereby closing the catalytic cycle.

Not surprisingly, in all the cases studied, the carbopalladation/amination sequence was totally regioselective, always yielding the desired 1,4-benzodiazepin-5-ones as the sole products. Indeed, a 9-*endo* type attack on the unsubstituted terminus of the allyl moiety to produce a benzo[1,5]diazoninone ring is expected to be much more disfavoured (Scheme 3).

Finally, to ascertain that the above cyclization strategy could be satisfactorily carried out with an *N*-protecting group synthetically more attractive than the tosyl function, the *N*-Boc **1c** and the *N*-nosyl analogues **1d** [25] were synthesized and submitted to the same domino protocol as above. Although the former derivative gave only a moderate yield of benzodiazepine, the *N*-nosyl one smoothly cyclised in high yield (Table 3) [26].

3. Conclusion

We have developed an original approach to 1,4-benzodiazepin-5-ones starting from *N*-allenamides of anthranilic acid. This was obtained designing a catalytic sequence wherein a C–C and C–N carbon bond are created in a single synthetic operation. Besides their intrinsic pharmacological interest, the obtained scaffolds represent an interesting DOS-compatible platform [27] amenable to modular synthesis (via the use of differently substituted anthranilic acids and/or allenyl moieties) as well as orthogonal protections. Furthermore, the vinyl moiety of the products lends itself to easy post-cyclisation modifications.

4. Experimental section

4.1. General information

DMSO was distilled over CaH_2 under reduced pressure. All other solvents were dried on a MBraun solvent purification system MB