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Total Synthesis of Rhazinilam through Gold-Catalyzed Cycloisomerization-Sulfonyl Migration & Palladium-Catalyzed Suzuki-Miyaura Coupling of Pyrrolyl Sulfonates

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Supporting Information Placeholder

ABSTRACT: We report the first general conditions for the challenging Suzuki-Miyaura reaction with pyrrole-related sulfonate coupling partners (24 examples, 60-97%). Bis(dichloro)bis(2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl) palladium(II) precatalyst ensures the high efficiency of the reaction. The total synthesis of rhazinilam, a monoterpene indole alkaloid, highlights such cross-coupling as well as the simple preparation of pyrrolyl sulfonates by *N*-to-*O* 1,5-sulfonyl migration catalyzed by gold(I) (15 examples, 54-93%).

Alkaloids constitute a huge family of natural products. Among them, monoterpene indole alkaloids exhibit a large structural diversity and a wide range of pharmacological properties.¹ This alkaloid subfamily has provided several useful anticancer compounds. Isolated from the plants *Rhazya stricta*, *Melodinus australia* and *Kopsia* sp., respectively growing in the desertic parts of Iraq and the Arabic peninsula and in Oceania, rhazinilam² is one of these anticancer alkaloids (Scheme 1, top). It exhibits taxol-like activity in inhibiting microtubule assembly and disassembly,³ and further studies revealed that it also promotes the formation of abnormal tubulin spirals.⁴ These unique biological activities in the low micromolar range (IC₅₀ 0.6-1.2 μM) together with a unique structure have initiated several total syntheses of rhazinilam and analogs, often aimed at developing new anticancer drugs.

Within the various approaches reported in the literature,⁵ the controlled formation of the tetrahydroindolizine core, the anilino-pyrrole motif or the quaternary center has represented the most important challenge.

The gold-catalyzed cycloisomerization-sulfonyl migration cascade we recently discovered⁶ offers a unique opportunity to design a new synthetic route to rhazinilam and related natural compounds (Step A, Scheme 1, bottom).⁷ This gold-promoted cascade could indeed efficiently provide the rhazinilam pyrrole core, ready for an unprecedented Suzuki-Miyaura-type coupling reaction (Step B). A further oxidative Heck-type reaction (Step C) between a prepositioned alkene function and

the pyrrole core would give the tricyclic structure ready for macrolactamization, while forming the quaternary center.⁸

Scheme 1. Planned Strategy towards the Synthesis of Rhazinilam Based on Gold-Catalyzed Cascade and Suzuki-Miyaura Coupling of Pyrrolyl Sulfonates.

This work: Improved & Extended Gold-Catalyzed Cyclization/Sulfonyl Migration

To implement this strategy, our gold-catalyzed cycloisomerization-sulfonyl migration cascade must first be extended to acyclic 1-aminobut-3-yn-2-ones to produce 1,2,4-trisubstituted pyrrolyl sulfonates. Second, the Suzuki-Miyaura coupling reaction of pyrrolyl tosylates and related sulfonates must be developed. Indeed, only a handful of such reactions

involving *N*-heterocyclic sulfonates other than triflate have so far been reported and none of pyrrolyl sulfonates (Scheme 2).⁹ We therefore investigated these reactions and we reported here our results, including the new palladium-catalyzed coupling of pyrrolyl sulfonates, as well as their application to a concise total synthesis of rhazinilam.

Scheme 2. Suzuki-Miyaura Palladium Coupling of *N*-Heteroaryl Tosylates with Boronic Acids.

In order to validate the above-mentioned strategy, step A was first investigated. Various *N*-alkylated *N*-sulfonyl 1-aminobut-3-yn-2-ones **1** were prepared from methyl glycinate (see Supporting Information), including examples carrying *N*-pent-4-enyl chain as models of the precursor required for the rhazinilam synthesis (Step C). They were then submitted to the conditions we developed for the gold-catalyzed cycloisomerization-sulfonyl migration reaction and various gold catalysts were briefly surveyed. Although the Gagosz catalyst (PPh₃AuNTf₂) gave good results for the formation of dihydropyrrolizines⁶, JohnPhosAuNTf₂ proved to be more efficient with acyclic as well as cyclic substrates **1** (Scheme 3). Within 5-10 minutes, they were converted to the expected sulfonylated pyrroles **2a-f** in high yields (80-93%). The yield was slightly lower with a simple *N*-benzyl chain due to the instability of compound **2d**. Because in the rhazinilam synthesis the steps B and C (Scheme 1) could be inverted, *N*-sulfonyl pyrrolidines and piperidines carrying a 1-oxo-2-propynyl chain were also prepared and submitted to the above-mentioned conditions. The expected sulfonylated di- or tetrahydro pyrrolizines or indolizines **2g-n** were efficiently produced in good to excellent yields.

It is worth noticing that such methodology is fully compatible with various sulfonyl groups, including tosylates (Ts), *para*-methoxybenzenesulfonates (Mbs), mesylates (Ms) and nosylates (Ns) which provide the best results (78-96%) generally within minutes, while triflates (Tf) were ineffective in this cascade (see **2l** vs **2h-k**). These results clearly enlarge the scope of our gold-catalyzed cycloisomerization-sulfonyl migration cascade and open the stage for the planned rhazinilam synthesis.

Scheme 3. Scope of the Gold(I)-Catalyzed Cycloisomerization-Sulfonyl Migration Cascade Starting from *N*-Sulfonyl 1-Aminobut-3-yn-2-ones **1**.

Ts = Tosyl; Mbs = 4-Methoxybenzenesulfonyl; Ms = Mesyl; Ns = Nosyl; Tf = Triflate.

The Suzuki-Miyaura reaction between boronic acids and pyrrolyl sulfonates **2** was then investigated. This cross-coupling was challenging considering the difficulty to perform the oxidative addition of Pd(0) to electron-rich *N*-sulfonylated pyrroles, and the ability of *N*-heterocycles to displace phosphine ligands to form stable palladium(II) complexes.¹⁰

The pyrrolyl tosylate **2h**, easily obtained in few steps on gram scale from proline, was selected for the optimization work (see Supporting Information). Applying the conditions reported for related *N*-heterocyclic tosylates (Scheme 2) did not give the expected products. Screening palladium sources and ligands revealed bis(acetonitrile)palladium dichloride and XPhos as the best combination toward an active catalyst. However, the base nature turned out to be crucial, as well as its concentration, in agreement with the delicate balance the base plays with the boron coupling agent and at the transmetalation step in Suzuki-Miyaura coupling.¹¹ Furthermore, reproducibility issues were faced (Eq. 1 in Scheme 4). Inspired by studies from the Hartwig and Buchwald groups, which showed that in certain couplings,¹² it is beneficial to independently prepare the actual catalyst rather than produce it in situ,¹³ we screened several preformed catalysts and found that PdCl₂(XPhos)₂ gave the best results in butanol-water in the presence of one equivalent of tetrabutylammonium hydroxide as base (Eq. 1 Scheme 4). Surprisingly almost unknown,¹⁴ PdCl₂(XPhos)₂ was easily obtained by heating bis(acetonitrile)palladium dichloride and XPhos in acetonitrile (Eq. 2 in Scheme 4).

With an effective catalyst and the right conditions in hand, we then explored the scope of this unprecedented transformation. Monocyclic as well as bicyclic pyrrolyl sulfonates were submitted to arylboronic acid in the presence of PdCl₂(XPhos)₂ as precatalyst and tetrabutylammonium hydroxide as base under microwave irradiation at 110 °C (Scheme 5).

Scheme 4. Limitation in Suzuki-Miyaura coupling and its Solution through the Synthesis of Bis(XPhos)palladium Dichloride as a Precatalyst.

Scheme 5. Scope of Suzuki-Miyaura Cross-Coupling from Various Pyrrolyl Sulfonates **2 and Boronic acids.**

^a Cumulative yields of *N*-pent-4-enyl and *N*-pent-3-enyl derivatives. Ts = Tosyl; Mbs = 4-Methoxybenzenesulfonyl; Ms = Mesyl; Ns = Nosyl; TBDPS = *t*-Butyldiphenylsilyl.

^a Cumulative yields of *N*-pent-4-enyl and *N*-pent-3-enyl derivatives. ^b Yield calculated by integration of the ¹H NMR spectrum of the crude product relative to an internal standard (dimethyl terephthalate). Ts = Tosyl; Mbs = 4-Methoxybenzenesulfonyl; Ms = Mesyl; Ns = Nosyl; TBDPS = *t*-Butyldiphenylsilyl.

Under such optimal conditions, the simple *N*-methyl pyrrolyl tosylates or 4-methoxybenzenesulfonates **2a-c** readily reacted with phenyl boronic acid and provided the expected coupling products **3a-b** in good to high yields. Rewardingly for the planned rhazinilam total synthesis, the coupling of **2a** with the non-protected anilinoboronic acid efficiently provided the 2-aminophenyl pyrrole **3c** in the highest yield. **3c** indeed corresponds to the key anilinopyrrole motif of the rhazinilam natural product family. The pyrrolyl tosylate **2a** could also be coupled with heteroaromatic boronic acids, leading to the corresponding thienyl and pyrimidyl pyrroles **3d-e** in good yields. Pyrrolyl sulfonates carrying *N*-benzyl **2d** or pent-4-enyl

chain **2e-f** were transformed into coupled compounds **3f-h** in high yields. Under the coupling conditions, isomerization of the double bond occurred for compounds **2e-f** leading to inseparable mixtures of 3 regio- and stereoisomers for both products **3g** and **3h**.

The dihydropyrrolizine or tetrahydroindolizine sulfonates (**3i-v**) we already obtained through our gold-catalyzed cycloisomerization-sulfonyl migration cascade⁶ could also be coupled with various boronic acids under the same conditions. Interestingly, *para*-methoxybenzenesulfonate and mesylate reacted almost as well as the corresponding tosylate, while the nosylate only gave low yield of the coupling product (see the **3j** series). The nosylate group turned to be sensitive to the applied basic conditions. Variations of the electronic density of the arylboronic acid coupling agent did not alter much the coupling efficiency, so far an electron-rich aryl was transferred (see **3n-s** vs **3j**). Mildly electron withdrawing substituents and even a fluorine were well tolerated (see **3o-p** vs **3j**) and only the strongly withdrawing nitro group diminished the coupling efficiency (see **3q** vs **3j**). As with monocyclic pyrrole sulfonate, the *ortho*-anilinoboronic acid efficiently provided the 2-aminophenyl dihydropyrrolizine **3r** in very high yield without the need of protecting group. The same was true for the coupling of the *ortho*-hydroxyphenylboronic acid, although the yield of the so-obtained 2-hydroxyphenyl dihydropyrrolizine **3s** was lower. The protected catecholboronic acid provided the expected coupling product **3t** again in high yield.

With the key two first steps of the planned rhazinilam synthesis (steps A and B in Scheme 1) ensured with model compounds, we then embarked on its total synthesis (Scheme 6). Two linear precursors **1o-p** were prepared in three steps from *N*-tosyl or *N*-4-methoxybenzenesulfonyl glycine methyl esters and the known *tert*-butyl (*E*)-4-ethylidene-7-iodoheptanoate¹⁵ compound respectively (See Supporting Information). The gold-catalyzed cycloisomerization-sulfonyl migration cascade was then performed starting from each derivative under the conditions mentioned above. The expected *N*-alkylated pyrrolyl sulfonates **2o-p** were efficiently (within 1 min) obtained in very high and similar yields.

From these compounds, the two routes were explored. First, Heck-type reaction (Step C in Scheme 1) which would provide the tetrahydroindolizine core of rhazinilam was tested before our Suzuki-Miyaura cross coupling (Step B in Scheme 1). The known conditions, some already used in the synthesis of rhazinilam and related natural products,¹⁶ only led to degradation. Eventually, a combination of solvents similar to those reported by Trauner,¹⁷ and with dioxygen as the oxidant at room temperature as in Gaunt's conditions,¹⁸ allowed formation of the cyclized products **4a-b**. However, careful analysis of the product structures revealed that the cyclization occurred at the less nucleophilic carbon 5 of the pyrrole instead of carbon 2,¹⁹ suggesting a C-H activation mechanism.²⁰ Furthermore, a large difference in efficiency was observed, as the *para*-methoxybenzenesulfonate **4a** provided the bicyclic product with high yield, while the tosylate **4b** did it only with low yield (76 vs 25%). Nevertheless, coupling **4a** with the unprotected 2-aminophenylboronic acid under our optimized conditions gave the coupling product **3w** in high yield within 30 min, and thus validated this step on rhazinilam-type compounds coupling.

Scheme 6. Total Synthesis of Rhazinilam.

Considering this selectivity issue and inspired by the Zakarian's total synthesis of rhazinilam based on the transannular cyclization of a halogenated 13-membered lactam¹⁵, the reverse sequence was applied to **2o-p**. Indeed, due to the macrolactam structure, the alkene moiety lies closer to carbon 2 than to carbon 5 of the pyrrole moiety, suggesting that the ring closure should take place at the desired position for the key Heck-type reaction. The coupling of **2o-p** with the unprotected anilino boronic acid provided the expected 2-aminophenyl pyrrole **3x** in excellent yield starting from the tosylate **2o**, but in lower yield from **2p**. The completion of the synthesis was achieved through macrolactamization, intramolecular oxidative Heck addition and hydrogenation of the resulting vinyl side chain. The macrolactam formation was readily performed according to Zakarian's conditions,¹⁵ furnishing **5** in high overall yields. After several trials, the intra-chain Heck-type reaction could only be performed at high temperature using the conditions developed for compound **4a-b**. This allowed the isolation of the expected cyclized product with a moderate yield. Hydrogenation of the latter under conventional conditions quantitatively provided rhazinilam.

In conclusion, we achieved a 16-step synthesis of rhazinilam in its longest linear sequence, which included the preparation of Zakarian's iodoheptanoate precursor¹⁵ from *tert*-butyl acrylate. This synthesis allowed us to set up the gold-catalyzed cycloisomerization-sulfonyl migration of *N*-alkylated *N*-sulfonyl 1-aminobut-3-yn-2-ones to 1,2,4-trisubstituted pyrrolyl sulfonates and the first palladium-catalyzed coupling of pyrrolyl tosylates and related sulfonates.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details, copies of spectra, and additional table of optimization conditions (PDF)

Crystallographic data for complex **3** (CIF, CCDC 1867782)

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Notes

The authors declare no competing financial interests.

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