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Diastereoselective Spirocyclization via Intramolecular C(sp^3)–H Bond Functionalization Triggered by Sequential [1,5]-Hydride Shift/Cyclization Process: Approach to Spiro-tetrahydroquinolines

Arup Bhowmik,[a] Sumit Das[a,b] Writhabrata Sarkar,[a] K. M. Saidalavi,[a] Aniket Mishra,[a] Anupama Roy,[a] and Indubhusan Deb[a]*

[a]Organic and Medicinal Chemistry Division, Indian Institute of Chemical Biology, 4-Raja S. C. Mullick Road, Jadavpur, Kolkata 700032, India. [b]Academy of Scientific and Innovative Research (AcSIR). indubhusandeb@iicb.res.in & indubhusandeb@gmail.com

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Abstract: A direct synthesis of spiro[5.5]and [5.4]-tetrahydroquinolines has been developed through C(sp^3)–H bond functionalization triggered by sequential [1,5]- hydride shift /cyclization sequence using *ortho* amino benzaldehydes and active methylene compounds such as 2-coumaranone, 4-hydroxycoumarin, 3-coumaranone, and 3-isochromanone. This protocol provides a Lewis acid catalyst-free straight forward one-pot reaction in cases of 2-coumaranone and 4-hydroxycoumarin, Lewis acid-catalyzed stepwise reaction for 3-coumaranone and 3-isochromanone to access a wide range of spiro-heterocycles in excellent to good yields and diastereoselectivity.

Keywords:[1,5]-hydride shift reaction; Lewis acid catalyst; Spirocycles; tetrahydroisoquinoline; 2-coumaranone; 3-isochromanone.

Introduction

Coumaranone containing scaffolds have drawn much attention since aeons due to their presence in many biologically relevant molecules such as naturally occurring isoaurones(**I**),[1] isoaurostatin[2] marginalin[3] pterocarposide[4] radulifolin-B,[5] Commiphoranes (**III**),[6] aurones[7] and spirocyclic Griseofulvin analogues (**IV**)[8] an orally active antimycotic drug (Figure 1).

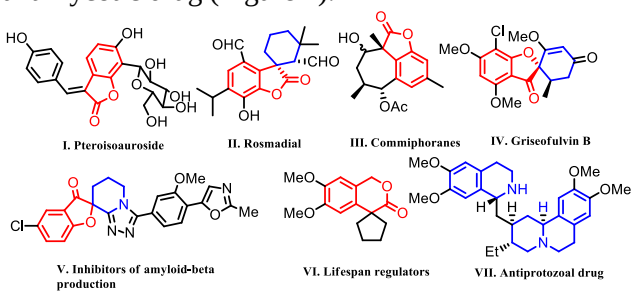


Figure 1. Representative example of relevant bioactive molecules

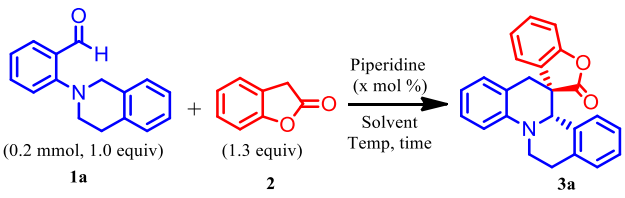
Various spirocyclic 2-coumaranones (**II**), benzofuran-3-one (**V**), 3-isochromanone (**VI**)[8b,d-j] derivatives, and isoaurones, aurones are well known pharmaceutically important compounds and natural products to exhibit excellent activity against different biological targets.[9-10] There has been enormous progress in the area of spirocyclic chemistry,[11] however the development of a highly stereoselective and atom-economic method for the construction of spirocyclic scaffold containing 2-coumaranones fused with *N*-heterocycles has hardly been explored.[12] Moreover, the presence of tetrahydroisoquinoline (THIQ) moiety, a powerful building block has given another dimension to construct a variety of bioactive molecules.[13] Recently, hydride transfer followed by cyclization sequence has become an attractive complementary approach for C(sp^3)−H bond functionalization. After groundbreaking findings by Reinhoudt,[14] the hydride shift reaction has been popularized mainly by Seidel,[15] Sames,[16] Akiyama,[17] Maulide,[18] and Li.[19]Over the past few decades, substantial efforts have been made by various research groups to develop varieties of hydride transfer/cyclization cascade reactions for the construction of structurally diverse complex molecules.[20] Yet, no protocol is available to

integrate these two alluring bioactive scaffolds till date, and 2-coumaranone and 3-isochromanone have not been used in hydride shift reaction cascade. Taking into account the importance of building blocks coumaranone, isochromanone, and 4-hydroxycoumarin scaffolds and in continuation to our ongoing interests toward the synthesis of densely functionalized (spiro) heterocycles via C–H bond activation,[21] we, herein report a straight forward and practical approach towards the synthesis of spiro-*N*-heterocycles via olefination, [1,5]-hydride transfer followed by cyclization strategy using corresponding aldehyde and coumaranone in one-pot operation.

Results and Discussion

We commenced the study by taking 1.3 equiv of 2-coumaranone (**2**) and 1 equiv of tetrahydroisoquinoline substituted benzaldehyde (**1a**) as the representative substrate using piperidine (20mol %) as a catalyst in toluene at 120 °C for 24 h. To our delight, the desired spiro[5.4]cyclic product **3a** as a major diastereomer was obtained spontaneously in 75% isolated yield in one-pot via olefin intermediate followed by [1,5]-hydride shift/cyclization sequence (Table 1, entry 1).

Table 1. Optimization of reaction condition[a]



entry	Piperidine (x mol %)	Solvent (6 mL)	Temp (°C)	time (h)	yield (%) of **3a**[b]
1	20	Toluene	120	24	75
2	20	Toluene	120	5	77
3	20	*m*-Xylene	150	5	71
4	20	Chlorobenzene	150	5	60
5	20	DMF	150	5	71
6	20	DMSO	150	5	65
7	20	DMAc	150	5	83
8	20	H_2O	100	12	40
9	20	CH_3CN	100	12	40
10	10	DMAc	150	5	75
11	30	DMAc	150	5	79
12[c]	20	DMAc	150	5	75
13	-	DMAc	150	6/5	70

[a]The reaction was carried out using 0.2 mmol of **1a** (1equiv) with 2-Coumaranone **2** (1.3 equiv) in presence of 20 mol % of piperidine. [b]Isolated yield. [c]Using 1.4 equiv of 2-coumaranone **2**.

A similar result was observed when the reaction time was reduced to 5 h (Table 1, entry 2). This result encouraged us to screen various solvents with moderate to high boiling points such as *m*-xylene, chlorobenzene, DMF, DMSO, DMAc, H_2O, CH_3CN (Table 1, entries 3-9) to elevate the reaction efficacy and DMAc was found to be more effective compared to others furnishing the product **3a** in 83% yield (Table 1, entry 7). Decreasing the loading of catalyst gave a diminished yield of 75% of **3a** (Table 1, entry 10) whereas increasing the loading of the catalyst showed almost similar results (Table 1, entry 11). Increasing the amount of 2-coumaranone (1.4 equiv) gave a slightly lowered yield of 75% of **3a** (Table 1, entry 12). A control experiment was conducted in the absence of piperidine and the formation of the product was observed and this result suggested that the piperidine is not essential for the reaction (Table 1, entry 13). However, a catalytic amount of piperidine accelerated the reaction to improve the yield of the product exquisitely.

With the standard conditions in hand, we investigated the scope of the cyclization reaction using 2-coumaranone **2** and the diverse *ortho*-amino benzaldehydes **1** as hydride donors (Scheme 1). In general, various substituted *ortho*-amino benzaldehydes are compatible with this reaction. Chloro substituted amino benzaldehyde produced the desired product **3b** in 98% yield with excellent diastereoselectivity (dr: 40:1). The dimethoxy containing tetrahydroisoquinoline substituted corresponding aldehyde **1c** underwent the reaction smoothly to afford **3c** in excellent yield with 25:1 diastereoselectivity. THIQ substituted 3-bromo pyridine 3-carboxaldehyde reacted well and delivered the product **3d** in excellent yield (98%) with excellent selectivity (dr: >40:1). Besides tetrahydroisoquinoline, several benzo-fused cyclic amines reacted well to provide molecular complexity. Tetrahydro-1H-benzo[c]azepane substituted aldehyde provided the single diastereomer of **3e** in moderate yield. However, dihydroisoindoline substituted aldehyde **1f** provided the product **3f** with moderate yield and selectivity. Apart from benzylamine, several cyclic and acyclic alkyl amines (α-CH_2 with respect to *N*) containing substrate underwent smooth hydride shift reaction. Pyrrolidine substituted aldehydes performed very well and produced **3g**, **3h,** and **3i** in moderate to good yields with excellent selectivity. Excellent diastereoselectivity was observed most probably due to high-temperature reaction conditions and presumably due to the formation of thermodynamic control product as a major diastereomer over the other.

Piperidine, azepane containing aldehydes afforded the products **3j-k** in excellent yields with poor diastereoselectivity. The slow rate of reaction was observed in the case of *N*-phenyl piperazine and morpholine substituted aldehyde. However, these two substrates provided the products as single diastereomer (**3l** and **3m**) for both cases. *N*, *N*-dibenzyl, and *N*, *N*-diethyl substituted aldehydes (**1n**

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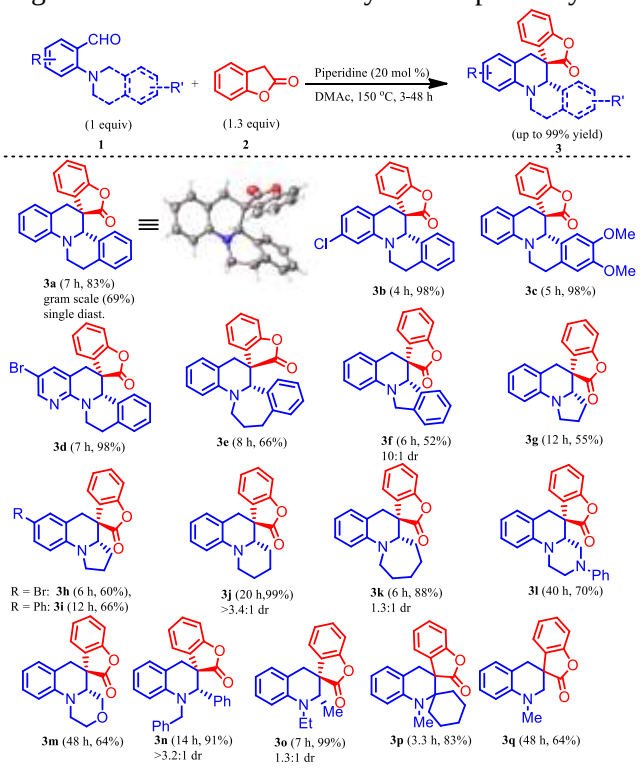
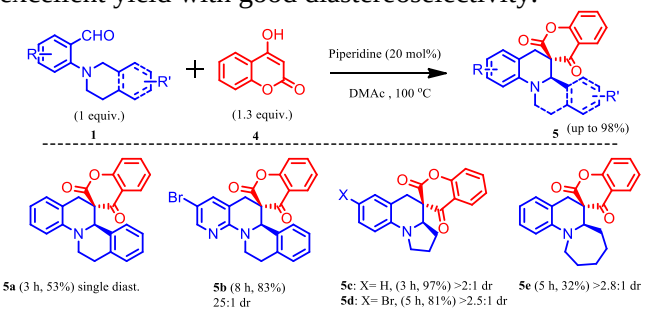
and **1o**) reacted well to provide the desired products **3n** and **3o** in good yield with poor dr. *N*-methyl-*N*-cyclohexyl and *N*, *N*-dimethyl substituted aldehydes generated the spirocyclic products **3p** and **3q** as single isomer in 83% and 64% yields respectively.



[a]Reaction conditions: all reactions were performed with a mixture of 1 (0.2 mmol), 2-coumaranone 2 (1.3 equiv) in DMAc (6 mL, 0.034M), dr given is calculated by 1H NMR.

Scheme 1. Scope of one-pot strategy for spiroheterocycles[a]

The substrate scope was further extended by taking another active partner 4-hydroxycoumarin **4**, as it is scarcely studied, reacting with various *ortho*-amino benzaldehydes **1** under a standard condition in one pot (Scheme 2) and gave the products **5a-b** in good to excellent yield with good diastereoselectivity.

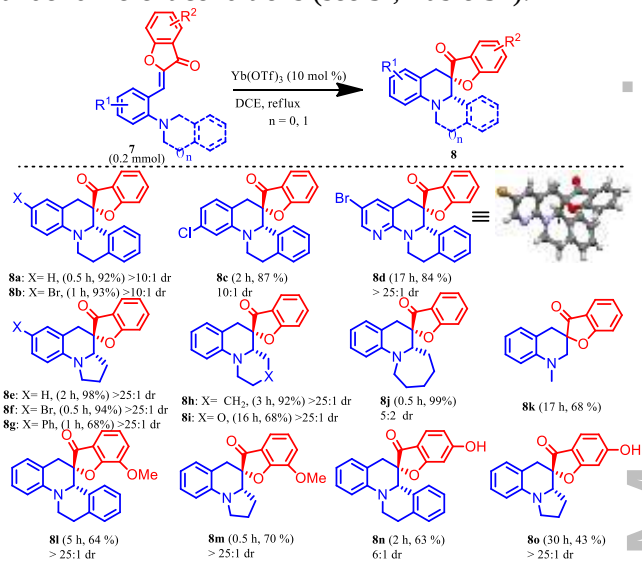


[a]Reaction conditions: all reactions were performed with a mixture of **1** (0.2 mmol), 4-hydroxycoumarine **4** (1.3 equiv) in DMAc (6 mL, 0.034M). dr given is calculated by ^{1}H NMR.

Scheme 2. Scope of cyclization of 4-hydroxycoumarine[a]

Then, the reactions were carried out with pyrrolidine, azepane substituted aldehydes, and afforded the products **5c-e** in moderate to good yield with poor diastereoselectivity.

On the basis of the above one-pot process, we turned our attention to the use of 3-coumaranone as another reacting partner for the synthesis of spiro heterocycles. Unfortunately, attempts towards the one-pot olefination followed by [1,5]-hydride transfer process using THIQ aldehyde **1** and 3-coumaranone **6** under various conditions including different solvents, temperature, Lewis acids remained unsuccessful. Hence, various olefins **7** were prepared, and the hydride shift followed by cyclization reaction was thoroughly optimized using **7a** as a model substrate under different conditions (see SI, Table S2).



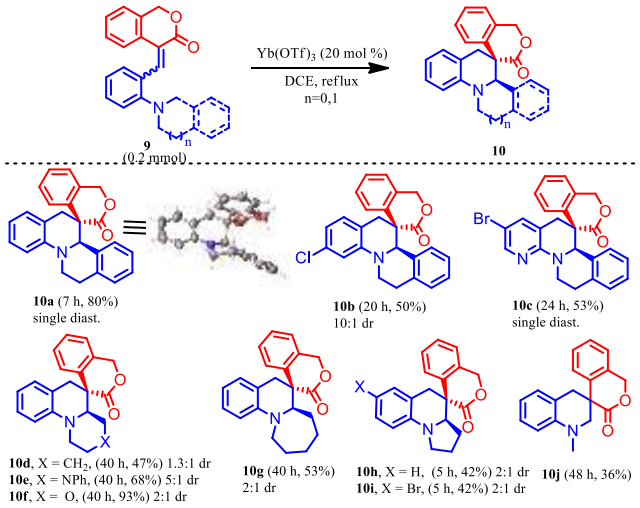
[a]Reaction conditions: all reactions were performed using olefin **7** (0.2 mmol), DCE (2 mL, 0.1M). dr given is calculated by ^{1}H NMR.

Scheme 3. Scope of cyclization of olefins **7**[a]

After performing the reaction under several parameters, we decided to explore the scope of substrates under the most efficient condition using 10 mol % $Yb(OTf)_3$ as a catalyst in DCE at reflux condition (Scheme 3). 3-Coumaranone containing THIQ substituted various olefins **7a-d** underwent smooth reaction to provide the desired cyclic products **8a-d** in good to excellent yields with high diastereoselectivity (84-93%). The structure of major diastereomer **8d** was confirmed by single-crystal X-ray analysis. To broaden the generality of the reaction, pyrrolidine, piperidine and morpholine substituted olefins **7e-g**, **7h** and **7i** were used and successfully afforded the products **8e-g**, **8h,** and **8i** in excellent yields with excellent selectivity. Formation of the product **8j** with excellent yield (99%) was observed in the case of azepane substituted substrate **7j**. Dimethyl substituted substrate **7k** afforded the product **8k** in good yield. Next, the reactions were

carried out with methoxy and hydroxy-substituted 3-coumaranone containing olefins **7l-o** and we obtained the products **8l-o** in moderate to good yields and diastereoselectivity.

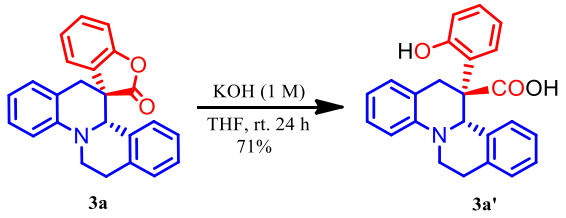
To further expand the scope of the reaction, for emphasizing this methodology mainly, we introduced another building block surrogate 3-isochromanone. This important pharmacophore was examined to construct a new class of spiro-heterocycles containing THIQ and 3-isochromanone moieties altogether. Despite their potential biological activities, no protocol is available to integrate these two pharmacophores to date. Delightfully, 3-isochromanone substituted olefins **9a** reacted to furnish the product **10a** as a single diastereomer in 80% yield in presence of 20 mol % of $Yb(OTf)_3$ under reflux temperature of the solvent DCE. The substrates **9b-j** successfully furnished the corresponding 3-isochromanone containing spiro heterocycles **10b-j** in moderate to good yields (Scheme 4) implying that pyrrolidine, piperidine, azepane, morpholine groups are well tolerable under this reaction condition.



[a]Reaction conditions: all reactions were performed using olefin **9** (0.2 mmol) in DCE (2 mL, 0.1M). dr is calculated by ^{1}H NMR.

Scheme 4. Synthesis of 3-isochromanone containing spiroheterocycles [a]

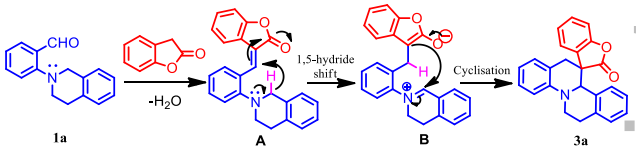
To demonstrate the synthetic utility, we successfully performed the transformation of **3a** to a new class of unnatural *β*-amino acid **3a'** by treatment with 1 M KOH in THF solvent (Scheme 5).



Scheme 5. Synthetic transformation of **3a**

Attempts toward the enantioselective version of the reaction under various reaction conditions using different chiral catalysts including chiral amines remain unsuccessful (SI-Table S3-5).

A plausible mechanism for this intramolecular 1,5-hydride shift reaction is depicted in Scheme 6. Initially, the ortho-amino benzaldehyde derivative 1a reacts with benzofuran-2-one through a Knoevenagel condensation reaction pathway to furnish substituted olefin A; next step is a Lewis-acid free or catalyzed intramolecular 1,5-hydride shift to form the spiro-heterocyclic product 3a through 6-endo-trig cyclization of **B**.



Scheme 6. Proposed reaction mechanism

Conclusion

In summary, we have developed a piperidine-catalyzed highly diastereoselective olefination followed by [1,5]-hydride shift/cyclization strategy to synthesize 2-coumaranone and coumarin functionalized novel spiro tetrahydroquinolines efficiently in good to excellent yields in one-pot. This strategy has been employed to synthesize 3-coumaranone and 3-isochromanone containing spiroheterocycles using Lewis acid-catalyzed [1,5]-hydride shift/6-endo cyclization sequences of corresponding olefins. Synthetic transformation of the product **3a** easily leads to the formation of a new class of bicyclic *β*-amino acid **3a'**. Our current studies are focused on asymmetric internal cascade redox neutral reaction using chiral organocatalyst for the efficient construction of molecular complexity, which may have potential pharmaceutical applications in future.

Experimental Section

General procedure for the synthesis of the final product 3a: To an oven-dried 25 mL round-bottom flask attached with condenser under nitrogen, 2-(3,4-dihydroisoquinolin-2(1H)-yl)benzaldehyde (**1a**) (0.2 mmol) and 2-coumaranone (**2**)(0.26 mmol) were taken, dissolved in anhydrous DMAc (6 mL) and the bath temperature was slowly increased to 150 °C. The reaction mixture was kept under the same temperature until the intermediate olefin was consumed completely as monitored by TLC. The solvent was removed from the organic layer by workup with EtOAc (2 x10 mL) and cold water; brine wash was needed. Then the organic layer passed through anhydrous Na_2SO_4 and concentrated under vacuo. Finally, it was purified by column chromatography on silica gel (230-400 mesh) using petroleum ether/ethyl acetate (99:1) as eluent to obtain the desired spiro-heterocyclic product **3a** in 83% (58 mg) yield.

Full characterization data and copies of relevant spectra of all new products are provided in the Supporting Information.

CCDC 1996347 (**3a**), CCDC 1996348 (**8d**), and CCDC1996349 (**10a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

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FULL PAPER

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Arup Bhowmik,[a] Sumit Das,[a,b] Writhabrata Sarkar,[a] K. M. Saidalavi,[a] Aniket Mishra,[a] Anupama Roy,[a] and Indubhusan Deb[a]*