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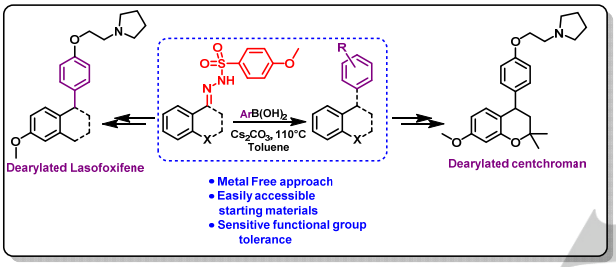
Versatile Synthesis of 4-aryl Chroman and 1-aryl Tetralins through Metal free Reductive Arylations

Gautam Panda,*[a], [b] Srinivas Lavanya Kumar M[b]

Abstract: A metal free approach was developed for accessing 4-aryl chromans and 1-aryl tetralins from their commercially available building blocks. This operationally simple protocol was well tolerated with existence of labile functional groups providing biologically relevant chemical libraries which are poised for their late stage modification. Dearylated analogues of drugs Ormeloxifene and Lasofoxifene were synthesized using this approach.



Introduction

4-Aryl chromans and 1-aryl tetralins are essential structural components which are generally found integrated into the cores of several secondary metabolites and pharmaceutically important molecules. Their clinical efficiencies were well documented[1] exhibhiting a diverse array of therapeutic contours thereby compelling reposition[2] in the drug discovery pipeline. Notable drug candidates in this realm includes centchroman (ormeloxifene)[3] and lasofoxifene[4] Fig:1, (**I**) and (**III**) which are potent non-steroidal selective estrogen receptor modulators (SERMs) and are currently being marketed. The prospective drug candidate NNC 45-0781 Fig: 1, (**II**)[5] developed for post-menopausal osteoporosis holds 4-aryl chroman in its pharmacophore. The flavonoid Myristinin A,[6] Fig:1, (**IV**) isolated from Myristica cinnamomea and Knema elegans, displays antifungal and DNA β-polymerase inhibitory activities. The anti-depressant sertraline[7] which belongs to the class of selective serotonin reuptake inhibitor also endorses 1-aryl tetralin skeleton. The antimitotic agent podophyllotoxin Fig:1, (**V**) has a very distinguished biological profile[8] and known as potent inhibitor of microtubule assemblage. Its semisynthetic derivatives[9] etoposide and teniposide were relatively less cytotoxic and are presently used as frontline cancer chemotherapeutics. The pauciflorol-F, caraphenol-B, ampelosine-D which are much familiar as the oligomers[10] of resveratrol shares this common congeners. The ethanolic extract from the bark of *M. robusta* constitutes several bioactive neolignans of this class.[11] The chiroptical studies[12] on these systems revealed that these molecules exhibited essential switching properties like dynamic helicity and thermal stability.

Accessing a divergent functional library of 4-aryl chromans and 1-aryl tetralins is however complemented with the synthetic limits. A careful literature study specifies that retrosynthetic deficiencies exist in accessing these widely acknowledged architectures through a unified approach. Their conventional synthesis[13] involves a 2 steps protocol; the addition of aryl Grignard or lithium on the chromanone/ tetralone skeletons and dehydrating them to their alkenes followed by Pd catalysed hydrogenation of these alkenes. The convergent approach

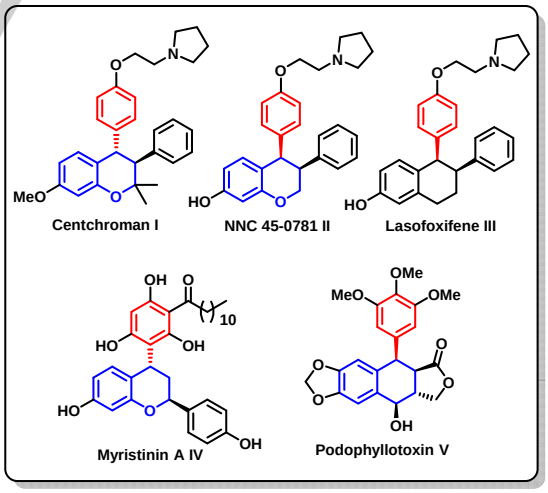


Fig:1 Some structurally important 4-aryl chromans and 1-aryl tetralins

(**a**, scheme-1) developed by Zanda[14] et al was an aryl sulfoxide based alkylation/cyclization sequence on electron rich aryl systems. Hajra et al demonstrated that rationally tethered alkenes[15] can be used to develop these architectures through lewis acid promoted halo-arylations (**b**, scheme-1). Urbano et al

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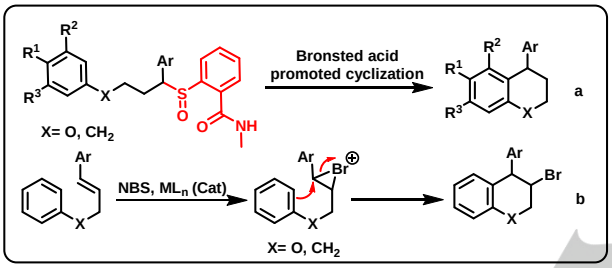
in an effort to synthesize 8-aryl-2-tetralones,[16] demonstrated the synthesis of 1-aryl tetralins by selective Birch reduction of 1-aryl-7-methoxynaphthalenes. In a pioneering report,[17a] K. A. Jorgenson developed diphenyl prolinol ether catalysed Friedel-Crafts cyclization cascade between α,β–unsaturated aldehydes and phenols to access the 4-aryl chromans. Later, this strategy was extended to the naphthols by Wang [17b] et al and to the α,β–unsaturated ketoesters.[17c] Pericas et al utilized a lewis acid[18] catalyzed cyclization of aryl glycidyl ethers for synthesizing 4-aryl 3-chromanols. Wang et al also synthesized these structures through one pot tandem process[19] employing a lewis acidic ionic liquid BPyCl–$SnCl_2{\cdot}2H_2O$. However, the synthesis of these 4-aryl chromans through orthoquinomethides[20] necessitates the choice of specially functionalized, relatively unstable substrates and requires stringent reaction conditions.



Scheme-1 Previously reported convergent strategies for developing 4-aryl chromans and 1-aryl tetralins

Given our ongoing efforts towards synthesizing chroman based scaffolds of medicinal and synthetic importance,[21] we undertook the objective of developing a unified approach to access diversely substituted 1-aryl tetralins and 4-aryl chromans and the related libraries from their carbonyl feedstock. The easily accessible hydrazones were demonstrated as versatile building blocks by several research groups.[22] In a seminal report, Barleunga[23] et al developed base induced reductive arylation of tosyl hydrazones with aryl boronic acids circumventing the necessity of transition metal catalysts. This approach was validated on a wide range of substrates in terms of both coupling partners where conventional organometallic reagents were proven incompatible. This coupling strategy was later highly generalized with α-heterocyclic aldehyde and ketone derived tosyl hydrazones and also with allyl, alkenyl and even alkyl boronic acids by several groups.[24] This strategy was extended to several C(sp^3)-heteroatom couplings such as C-O,[25] C-S,[26] C-F, C-N,[27] C-P[28] systems. Accordingly, we anticipated that tosyl hydrazones would be a very good precursors to develop a relatively mild and operationally simple protocol for establishing this highly demanding C(sp^3)−C(sp^2) bonds and to develop a library with an access to late stage functional group modifications.

Results and Discussion

All the sulfonyl hydrazones of chromanones and tetralones were prepared as per standard procedures.[23, 24c] At the outset, we engaged chroman derived tosyl hydrazone **1aA** with phenyl boronic acid **2a** for the title transformation under Barleunga conditions,[23] (Table-1, entry-1) resulting 42% of 4-aryl chroman **3a**. $CaCO_3$ couldn't initiate any tosyl hydrazone decomposition whereas Ag_2CO_3 resulted in complete decomposition of starting materials. K_3PO_4 promoted this thermolytic cross-coupling about 39%, but Cs_2CO_3 seemed optimal (Table-1, entry-4, 5). Organic bases remained ineffective and N-alkylated products became dominant when any nucleophilic base was used (Table-1, entry-6, 7).[29,30,31,32] Molecular sieves and additives such as $(n\text{-Bu})_4NI$, KI were already proved detrimental for this coupling.[24c,29] Temperatures below 110°C resulted in either prolonged reaction times or poor conversions. (Table-1, entry- 8, 9). pKa of the conjugate acid that corresponds to the sulfonyl group on the hydrazone had a remarkable effect on the product outcome. With electron-poor aryl sulfonyl hydrazones, rate of decomposition becomes faster but either alkene or dimerized products were observed at larger extent. (Table-1, entry- 10, 11).[31] Electron-rich sulfonyl hydrazones needed longer reaction times but yields appeared optimal and *p*-methoxyphenyl sulfonyl hydrazone (pmp) **1ad** analogue underwent this metal free coupling reaction resulting 68% of chroman. This prompted us in using 4- methoxybenzene substituted sulfonyl hydrazones in subsequent reactions. A short screen was set using the solvents having boiling range higher than 90 °C. Reaction became sluggish with DMSO and DMF (Table-1, entry- 14, 15). Yields were moderate while using solvents such as nitromethane and fluorobenzene (Table-1, entry- 17, 18). Although dioxane resulted in comparable yield, optimal conditions were chosen considering toluene as solvent, and Cs_2CO_3 as base.

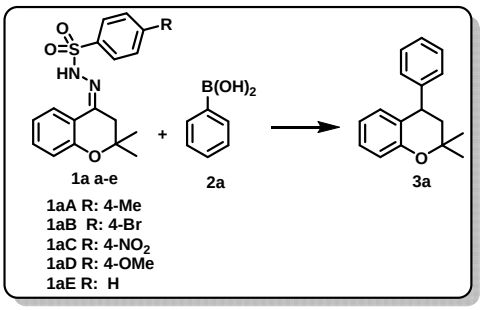


Table 1. Optimization studies

Entry[a]	Hydrazone	Solvent	Base	Time (h)	Yield (%)[b]
1	**1aA**	Toluene	K_2CO_3	12	42
2	**1aA**	Toluene	$CaCO_3$	24	NR

3	**1aA**	Toluene	Ag_2CO_3	14	ND[c]
4	**1aA**	Toluene	Cs_2CO_3	10	58
5	**1aA**	Toluene	K_3PO_4	14	39
6	**1aA**	Toluene	KO^{t}Bu	15	-
7	**1aA**	Toluene	NaOH	24	<10[d]
8	**1aA**	Toluene	Cs_2CO_3	20	51[e]
9	**1aA**	Toluene	Cs_2CO_3	36	26[f]
10	**1aB**	Toluene	Cs_2CO_3	7	34
11	**1aC**	Toluene	Cs_2CO_3	3	<10[c]
12	**1aD**	**Toluene**	**Cs_2CO_3**	**14**	**76**
13	**1aE**	Toluene	Cs_2CO_3	10	48
14	**1aD**	DMF	Cs_2CO_3	18	19
15	**1aD**	DMSO	Cs_2CO_3	10	-[c]
16	**1aD**	Dioxane	Cs_2CO_3	10	68
17	**1aD**	Nitro methane	Cs_2CO_3	14	40
18	**1aD**	Floro benzene	Cs_2CO_3	12	64

[a] Reaction conditions: 0.5 mmol of **1a(A-E)**; 0.75 mmol of boronic acid; 1 mmol base, sealed tube, 110 ºC [b] Isolated yields [c]decomposed starting materials or complex reaction mixture [d] N-alkylated products observed [e] Reaction performed at 90 ºC [f] Reaction performed at 70 ºC, NR: No Reaction, ND: Not Determined.

With the optimal conditions, the generality of this metal free coupling reaction was evaluated. Hydrazones synthesized from both commercially available and tailor-made chromanones were subjected to this reductive arylations. A range of boronic acids including electron rich, heteroaryl and even halogen substituted boronic acids participated in this coupling providing moderate to excellent yields. However, electron rich boronic acids resulted in slightly better yields (Table 2; **3ac**, **3ad**, **3af**, **3di**, **3fc**). Electron rich chroman system suffered from comparatively less yields (Table 2; **3be**, **3bb**, **3bg**) probably due to the reluctance of stabilized carbenes to participate in the coupling. Accordingly, chromans bearing electron deficient substitutions such as F, Br, OTs (**1d**, **1c**, **1f**) underwent this reaction in good yields (Table 2; **3df**, **3di, 3ce**, **3cj**, **3fc, 3fe**). Functional groups such as OTs, Br survived this coupling conditions which are usually found to be incompatible with typical metal promoted couplings, providing a handle for late stage functional group modification and thus generating diverse chemical libraries having sensitive groups. The sterically demanding chromans (**3eh, 3ee**) could also be accessed utilising this coupling approach. Chroman systems such as **3b** and **3d** typically constitute the cores of drugs Ormeloxifene and NNC 45-0781 providing direct access to their libraries.

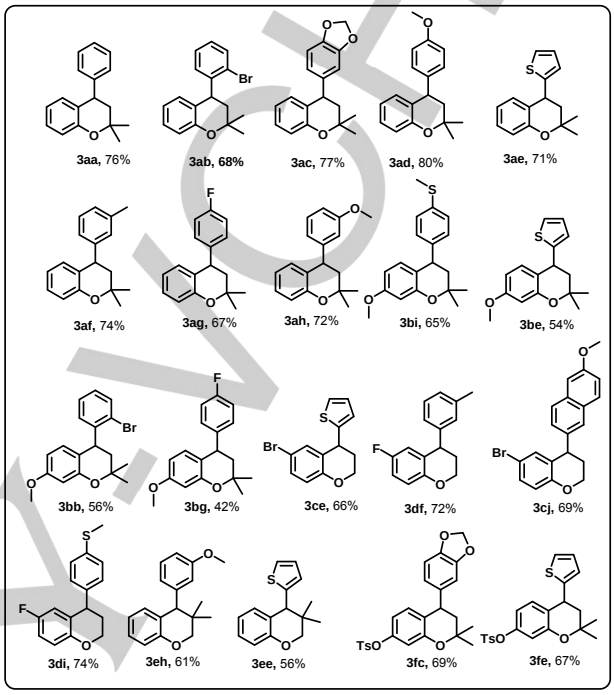


Table:-2 Synthesis of 4-aryl chromans from reductive arylation of hydrazones

After successfully testing this methodology in synthesizing 4-aryl chromans, we intended to expose the hydrazones derived from 4-methoxy benzene sulfonyl hydrazide and

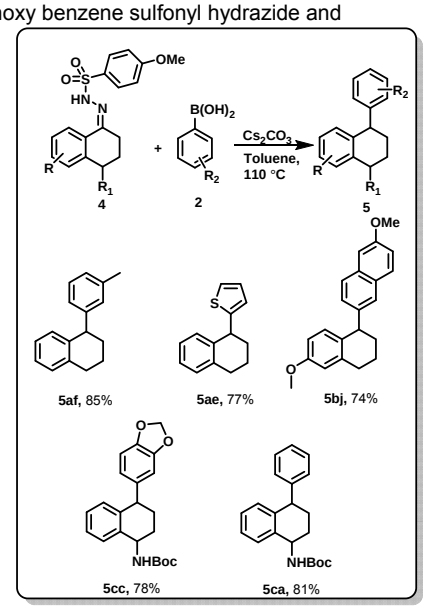
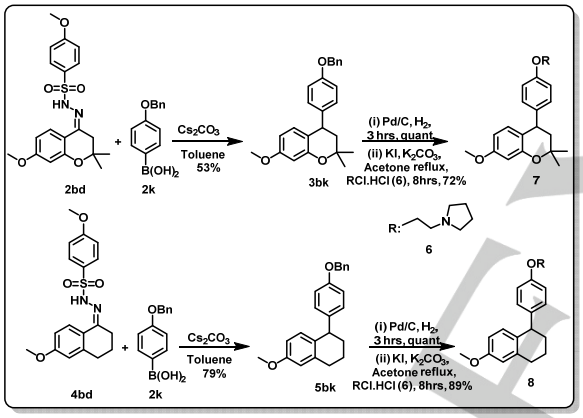


Table:-3 Synthesis of 1-aryl tetralins from hydrazones

tetralones to this coupling conditions. Delightfully, several hydrazones underwent this coupling reaction to give products having relatively labile functionalities (Table:3) in excellent yields. Tetralin hydrazones served as better coupling partners than chromanones resulting in slightly higher yields as the later suffers from assistance of ethereal oxygen.

This approach can be conveniently explored for constructing the dearylated analogues of drug molecules ormeloxifene and lasofoxifene. Hydrazone systems **1b**, **4b** here serve as viable precursors for assembling this essential $C(sp^3)-C(sp^2)$ bond targeting these valuable architectures. Under optimal conditions, hydrazones **2bd**, **4bd** were made to react with synthetically prepared boronic acid **2k** (scheme: 2) for installing aryl pendant on the cores of these hydrazones resulting **3bk** and **5bk** respectively. The **3bk** and **5bk** upon debenzylation were alkylated with chloroethyl pyrrolidine hydrochloride **6** leading to dearylated ormeloxifene **7** and lasofoxifene **8** respectively with high yields.



Scheme:2 Synthesis of dearylated analogues of Ormeloxifene and Lasofoxifene

Conclusions

We developed a metal free approach for the synthesis of 4-aryl chromans and 1-aryl tetralins from their carbonyl feedstock. With easily accessible hydrazones, this strategy displayed a very good propensity to engage a range of aryl boronic acids to give highly valuable 4-aryl chromans and 1-aryl tetralins. This approach tolerated a relatively labile functionality allowing access to their modification at later stages. Chromans **3b**, **3c** and **3d** constitute the core of the Ormeloxifene and NNC 45-0781 respectively while tetralin systems **5b** represent the libraries of Lasofoxifene. This versatile methodology can also be utilized for assembling the tetralin and chroman core of other related drugs.

Experimental Section

General procedure B for the preparation of 4-aryl chromans and 1-aryl tetralins:

To the 0.5 mmol of hydrazone, was added 0.75 mmol of boronic acid and 1 mmol Cs_2CO_3 followed by 2 ml toluene in a screw-capped vial. The reaction mixture was sealed under N_2 atmosphere and was allowed to heat at 110ºC and TLC was monitored. After the completion of reaction, toluene was evaporated and brine solution was added to the reaction mixture. It was extracted with DCM and dried over Na_2SO_4. Purification over column chromatography resulted final compounds.

General procedure C for the debenzylation:

To an oven dried RB fitted with the septum, 1 mmol of benzopyran or tetralin was dissolved in methanol under nitrogen atmosphere and then added 0.1 mmol of Pd/C which was further degassed and backfilled with nitrogen. Then hydrogen was introduced slowly turning off the nitrogen supply and reaction was ran for 3 hrs. Within 4 hrs starting material was consumed as evidenced from TLC and reaction mixture was filtered through celite bed. The filtrate was concentrated resulting in debenzylated analogue quantitatively. The products were utilized for subsequent reaction without any purification.

General procedure D for the alkylation with 1-(2-Chloroethyl)pyrrolidine:

To the 1 mmol of debenzylated analogue dissolved in acetone, was added 2.2 equiv of K_2CO_3 and 1.05 equiv of 1-(2-chloroethyl)pyrrolidine hydrochloride and refluxed overnight. TLC was monitored and after the consumption of starting material, acetone was distilled off. Reaction mixture was partitioned between brine and EtOAc. Organic layer was collected, dried over Na_2SO_4, concentrated and column chromatography was performed.

General procedure E for the preparation of (4-(benzyloxy)phenyl)boronic acid 2k:

To the oven-dried RB equipped with magnetic stir-bar sealed with septum, was added 1.0 mmol of 1-(benzyloxy)-4-bromobenzene in dry THF. At -78ºC, about 1.5 equiv of 2M n-BuLi was added and stirred at that same temperature for 1 hr. Later, about 1.2 mmol of trimethyl borate was added and reaction was allowed to stir for 8 hrs at ambient temperature. Upon the completion of reaction as confirmed by TLC, it was quenched with sat. NH_4Cl solution and extracted with EtOAc 3 times. Organic layer was dried under sodium sulphate and concentrated. Column chromatography was performed.

1-(2-(4-(7-methoxy-2,2-dimethylchroman-4-yl)phenoxy)ethyl)pyrrolidine 7:

Following the experimental procedure C, benzopyran 3bk was debenzylated resulting the hydroxyl counterpart of 3bk which was subsequently utilized for the alkylation reaction. The chroman analogue 7 was obtained after an overnight reflux following the experimental procedure D as colorless oil in 85% yield. R¬f = 0.5 (6% methanol/DCM). 1H NMR (400 MHz, CDCl3, 25oC): δH 7.09 (d, J= 8.00 Hz, 2H), 6.87 (d, J= 7.80 Hz, 2H), 6.63 (d, J= 8.26 Hz, 1H), 6.38-6.34 (m, 2H), 4.12-4.06

(m, 2H), 3.98-3.95 (m, 1H), 3.75 (s, 3H), 2.92 (t, J= 5.64 Hz, 2H), 2.64 (bs, 4H), 2.00-1.89 (m, 2H), 1.82 (bs, 4H), 1.43 (s, 3H), 1.35 (s, 3H) ppm. 13C NMR (100 MHz, CDCl3, 25 oC): δC 159.31, 157.55, 154.85, 137.33, 130.37, 129.53, 117.21, 114.63, 107.09, 101.48, 74.94, 66.99, 55.20, 55.10, 54.68, 43.77, 38.53, 29.95, 24.25, 23.49 ppm.

1-(2-(4-(6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy)ethyl) pyrrolidine 8:

Following the experimental procedure C, tetralin 5bk11 was debenzylated resulting the hydroxyl counterpart of 3bk which was subsequently utilized for the alkylation reaction. The tetralin analogue 8 was obtained after an overnight reflux following the experimental procedure D as colorless oil in 80% yield. R¬f = 0.5 (4% methanol/DCM). 1H NMR (400 MHz, CDCl3, 25oC): δH 6.98 (d, J= 8.25 Hz, 2H), 6.82 (d, J= 8.25 Hz, 2H), 6.74 (d, J= 8.25 Hz, 1H), 6.65-6.59 (m, 2H), 4.08 (t, J= 5.70 Hz, 2H), 4.00-3.99 (m, 1H), 3.76 (s, 3H), 2.90-2.78 (m, 4H), 2.62 (bs, 4H), 2.11-2.09 (m, 1H), 1.87-1.71 (m, 7H) ppm. 13C NMR (100 MHz, CDCl3, 25 oC): δC 157.57, 157.09, 139.94, 138.68, 132.01, 131.11, 129.57, 114.27, 113.22, 112.03, 66.96, 55.17, 55.14, 54.67, 44.09, 33.53, 30.14, 23.50, 20.96 ppm.

Acknowledgements

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Keywords: Chromans • Tetralins • Metal free coupling • Hydrazones • Reductive arylation

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