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TfOH catalyzed synthesis of 1-substituted tetrahydrocarbazoles

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ABSTRACT

Synthesis of 1-substituted tetrahydrocarbazole is accomplished by TfOH catalyzed reaction of 3-substituted indoles tethered with secondary and tertiary alcohols. The reaction was generalized for a variety of substrates and was extended to the synthesis of 2,3,3a,6-tetrahydro-1*H*-pyrido[3,2,1-*jk*]carbazole and carbazoles.

Introduction

Tetrahydrocarbazoles and carbazoles are ubiquitous structural units found in a plethora of *bio*-active natural products (Fig. 1) [1]. Tetrahydrocarbazoles also serve as key precursors for the synthesis of carbazole containing natural products.

Traditional way of synthesizing tetrahydrocarbazole is the Fischer-indole reaction of cyclic ketones with arylhydrazines [2]. In recent years, most of the methods for the synthesis of tetrahydrocarbazoles are based on transition metal catalyzed reactions that require pre-functionalization, high catalyst loading, harsh reaction conditions and multi-step sequence for the preparation of the substrate [2–5]. Some of the key methods for the synthesis tetrahydrocarbazoles include the use of palladium, platinum, iridium and gold catalyzed reactions involving carboalkoxylation of 2-susbtituted alkenyl indoles (Fig. 2) [3,4]. Similarly organocatalytic Friedel-Craft's type alkylation of 2-substituted indolyl-α,β-aldehydes and transition metal catalyzed allylic alkylation of 2/3-substituted indoles are shown to yield tetrahydrocarbazoles. Very recently Nielsen and Zhang groups have reported phosphoric acid catalyzed synthesis of tetrahydrocarbazoles, limited only for the synthesis of indole susbstitution [4a,b]. Application of Diels-Alder type reactions are also reported for the synthesis of tetrahydrocrabazoles [5]. Török and co-workers used TfOH to synthesize *N*-phenylsulfonyl pyrrole, indole and carbazoles in one pot fashion starting from primary sulfonamides [6n]. Very recently, during the preparation of this manuscript, Beeraiah and Tharra reported AgOTf/TsOH catalyzed cycloisomerization of 3-susbtituted indoles for the synthesis of carbazoles *via* the tetrahydrocarbazole. However they failed in isolating the tetrahydrocarbazole intermediate [6o]. As evident from the above metal catalyzed reactions rely on the use of substrates possessing functionalized alcohols at the 2,3 positions of indole. However use of 3-substituted indolylbutanols is not explored in literature for the synthesis of tetrahydrocarbazoles [6d,7a,b].

In a solitary example Zheng et al. [6d] have demonstrated the synthesis of tetrahydrocarbazole from indolylphenylbutanol *via* a three step protocol during their mechanistic investigation concerning the stereoselective migration of spiroindolenines. In order to develop a new sophisticated methodology, it was reasoned that the formation of a carbocation from indole-3-butanol would lead to the spiroindolenines which would rearrange to form the tetrahydrocrabazole. Herein, it is disclosed the efforts concerning the transition metal free, Brønsted acid catalyzed, Friedel-Craft's type reaction for the divergent synthesis of tetrahydrocarbazoles starting from simple 3-substituted indole butanols **1** (Scheme 1).

Accordingly, the investigations commenced with the preparation of required alcohols **1a**–**f** from the Weinreb amide **3** synthesized [7] from commercially available indole-3-butyric acid (**2**). Addition of different Grignard or organolithium reagents to **3** yielded the ketones **4a**–**f** which on reduction with $NaBH_4$ rendered the required alcohols **1a**–**f** in good to excellent yields (Chart 1).

After accomplishing the synthesis of the required alcohol **1a**–**h**, optimization of reaction conditions for the formation of tetrahydrocarbazole **5a** from **1a** was examined. Reaction of the alcohol **1a** with 10 mol% of $FeCl_3{\cdot}6H_2O$ as catalyst afforded the product

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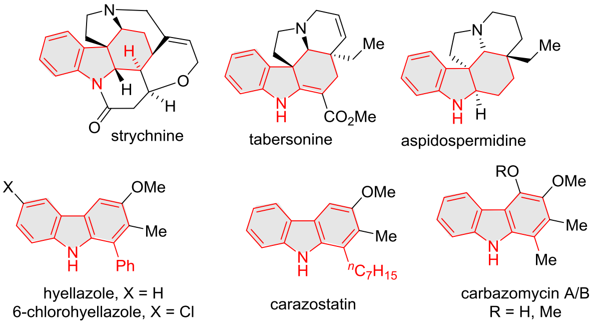
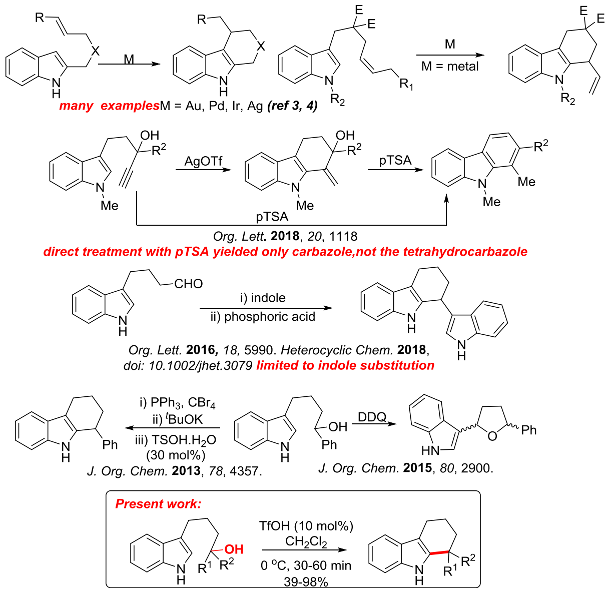


Fig. 1. Natural products having tetrahydrocarbazole and carbazole frameworks.



Scheme 1. Selected literature reports on tetrahydrocarbazole synthesis.

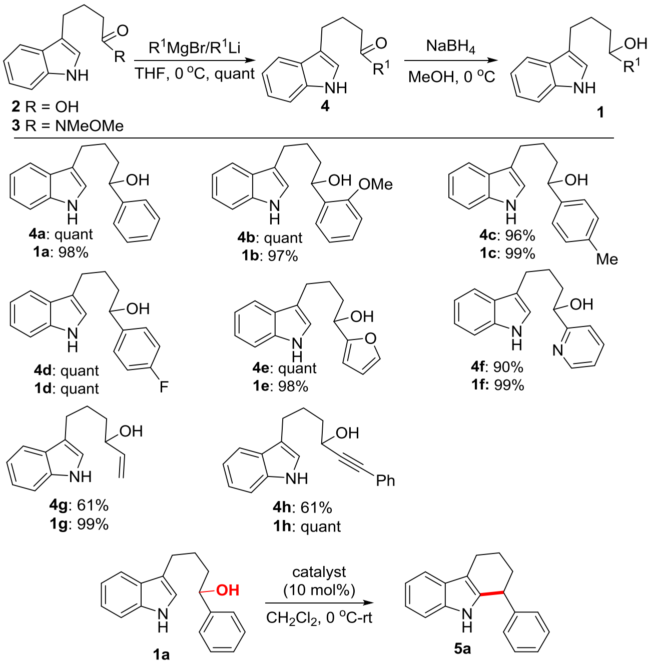


Chart 1. Synthesis of alcohols **1a**–**f**.

in 82% yield. When the catalyst was changed from $FeCl_3 \cdot 6H_2O$ to Brønsted acid such as triflic acid, the reaction proceeded with shorter reaction time and an improved yield of 98% of the product was observed. Reaction with *p*-TSA was incomplete and the product was obtained in 32% yield with 64% recovering of starting material. However, reaction with $BF_3 \cdot OEt_2$ and TMSOTf afforded the product in quantitative yield. No reaction was observed with camphor sulphonic acid, acetic acid and trifluoroacetic acid. All the results are summarised in Table 1.

After examining the reaction conditions, TfOH was chosen as the suitable catalyst since it produced excellent yield of the tetrahydrocarbazole in shorter reaction time. With this optimized condition synthesis of various tetrahydrocarbazoles were attempted.

Alcohols **1b**–**d** were subjected to reaction with catalytic amount of TfOH in CH_2Cl_2 and afforded the products **5a**–**d** in good to excellent yields (Chart 2). Acid sensitive heteroaromatic (furyl) substituted alcohol **1e** furnished the tetrahydrocarbazole **5e** in almost quantitative yield. Incidentally, reaction of the alcohol **1f** containing the pyridine group did not yield the desired product. Performing the reaction with the allylic and propargylic substituted alcohols **1g**–**h** also furnished the tetrahydrocarbazoles **5g** and **5h** respectively. It is interesting to note that during the course of reaction no isomerisation of double bond in presence of TfOH was observed and the alkyne did not undergo any hydroalkoxylation. It is worth noting that the tetrahydrocarbazole **5g** was prepared by Bandini et al. in a multi step sequence starting from 3-indolylpropanol [6c].

At this stage, we intended to investigate the reaction of tertiary alcohols derived from **4** in the formation of tetrahydrocarbazoles. Accordingly, addition of vinylmagnesium bromide to the phenyl ketone **4a** furnished the tertiary alcohol **1i** in quantitative yield. Addition of vinylmagnesium bromide to the ketones resulting from the addition of PhMgBr/EtMgBr to *N*-allyl Weinreb amide **6** gave the tertiary alcohols **1j**–**k**. Reaction of excess methylmagnesium bromide with the ester **7** furnished the known tertiary alcohol **1l** in 99% yield (Scheme 2).

Table 1
Synthesis of tetrahydrocarbazole **5a** from **1a**.

Entry	Catalyst	Time (h)	% Yield of **5a**
1	$FeCl_3 \cdot 6H_2O$	2	82
2	TfOH	0.5	98
3	*p*-TSA	2	32
4	$BF_3 \cdot OEt_2$	2	99
5	TMSOTf	1.2	99
6	CSA	2	NR
7	Acetic acid	2	NR
8	TFA	2	NR

NR: No Reaction.

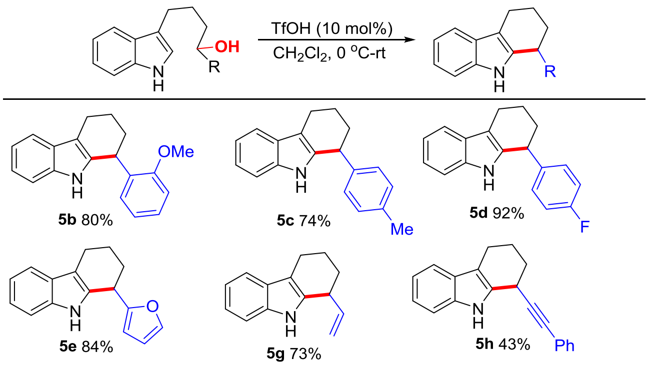


Chart 2. Synthesis of tetrahydrocarbazoles: Substrate scope.