JOC Note

Brønsted Acid Mediated Tandem Diels−Alder/Aromatization Reactions of Vinylindoles

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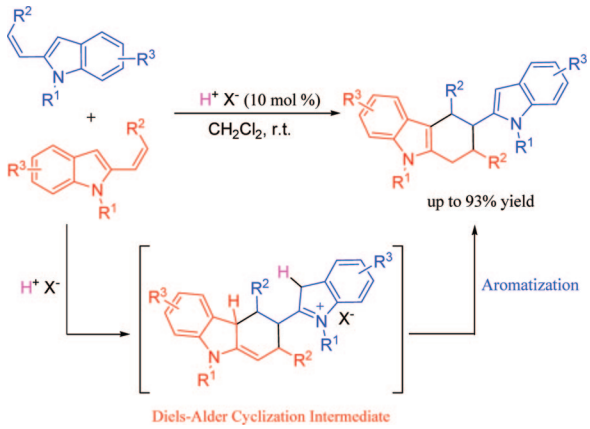

A Brønsted acid catalyzed tandem Diels−Alder/aromatization reaction of 2-vinylindoles has been developed. The reaction provides a highly efficient and concise approach to 3-indolyl-substituted tetrahydrocarbazoles with various substituents in high yields under mild conditions.

The development of new catalytic transformations for the construction of "privileged" structural motifs presented in biologically active compounds or natural isolates is of considerable current interest.[1] Many advances in this endeavor have focused on metal-catalyzed tandem, domino, or cascade reactions, in which multiple bond formations can be realized in a highly concise fashion in contrast to traditional "step-by-step" operations.[2] More recently, significant efforts have been made to develop organocatalytic variants of such processes.[3,4] In this context, the employment of Brønsted acids as catalysts has proven to be highly popular in a variety of reactions because of their facile accessibility, easy operation, and stability against moisture and oxygen.[5] Despite advances,[6] the search for Brønsted acid promoted tandem sequences that allow increasingly rapid access to structural complexity remains a preeminent goal.

The tetrahydrocarbazole architecture widely exists in various naturally occurring alkaloids and synthetic analogues of medicinal importance,[7−9] some of which can be potentially used

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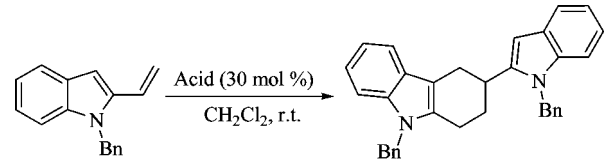
as tumor growth inhibitors and protein kinase C inhibitors.[10] As a consequence, many elegant methods for the preparation of various tetrahydrocarbazole derivatives have been developed in the past years,[11] including reductive cyclization of 2-nitrobiphenyl,[11q−s] Pd-catalyzed oxidation cyclization of 3-(3′-alkenyl)indoles,[11t] intramolecular arylation of *N*,*N*-diaryl-amines,[11u,v] and alkyllithium-mediated intramolecular anionic cyclization.[11w] However, many of these methods involve harsh reaction conditions, expensive reagents, complex handling, and low yields of products. Thus, it was desirable to develop operationally simple, more efficient, and practical catalytic approaches for the construction of tetrahydrocarbazoles. As part of our ongoing project on the synthesis of carbo- and heterocyclic compounds,[12] we report herein a straightforward method for the preparation of 3-indolyl-substituted tetrahydrocarbazole derivatives by trifluoroacetic acid (TFA)-catalyzed tandem Diels−Alder/aromatization reactions of 2-vinylindoles.

Initial studies were focused on examining the feasibility of the tandem reaction and at optimizing reaction conditions that could be applied to various vinylindoles. The reaction of 1-benzyl-2-vinyl-1*H*-indole (**1a**) was chosen as a model reaction and a series of Brønsted acid catalysts (Table 1) were tested. The catalyst screening indicated that trichloroacetic acid, *p*-toluenesulfonic acid monohydrate, trifluoromethanesulfonic acid, perchloric acid, and (±)-camphorsulfonic acid could efficiently promote the transformation to generate 9-benzyl-3-(1-benzyl-1*H*-indol-2-yl)-2,3,4,9-tetrahydro-1*H*-carbazole (**2a**)

TABLE 1. Optimization of Brønsted Acid Catalysts in the Tandem Diels−Alder Cyclization/Aromatization Sequence[a]

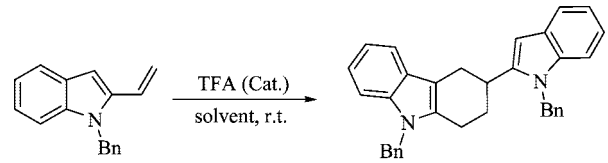


1a **2a**

entry	acid	time	yield (%)[b]
1	Cl_3CCO_2H	70 min	68
2[c]	$TsOH·H_2O$	50 min	61
3[d]	TfOH	30 min	72
4	$HClO_4$	55 min	96
5[e]	(±)-CSA	60 min	90
6	$NCCH_2CO_2H$	7 h	95
7	TFA	3 min	94
8	CH_3CO_2H	72 h	tr
9[f]	DNBA	72 h	tr
10[g]	(±)-BNP-H	120 h	tr

[a] Reaction conditions: **1a** (0.25 mmol), acid (0.075 mmol), CH_2Cl_2 (0.5 mL). [b] Isolated yield. [c] $TsOH·H_2O$: *p*-toluenesulfonic acid monohydrate. [d] TfOH: trifluoromethanesulfonic acid. [e] (±)-CSA: (±)-camphorsulfonic acid. [f] DNBA: 3,5-dinitrobenzoic acid. [g] (±)-BNP-H: (±)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate.

TABLE 2. Effect of Solvent and Catalyst Loading on Tandem Diels−Alder/Aromatization of 1a[a]



1a **2a**

entry	solvent	TFA (mol %)	time (min)	yield (%)[b]
1	$CHCl_3$	30	5	68
2	$ClCH_2CH_2Cl$	30	5	70
3	CH_2Cl_2	30	3	94
4	toluene	30	5	70
5	CH_3CN	30	30	82
6	Et_2O	30	300	53
7	*t*-BuOMe	30	300	43
8[c]	DMF	30		NR
9[c]	MeOH	30		NR
10[c]	*i*-PrOH	30		NR
11	CH_2Cl_2	10	5	92
12	CH_2Cl_2	5	60	83

[a] Reaction conditions: **1a** (0.25 mmol), TFA (0.0125−0.075 mmol), solvent (0.5 mL). [b] Isolated yield. [c] No reaction.

in good to excellent yields (Table 1, entries 1−5). In particular, TFA proved to be the most effective catalyst for this tandem Diels−Alder/aromatization reaction in dichloromethane at room temperature in terms of the yield (94%) and the reaction time (3 min) (Table 1, entry 7). Cyanoacetic acid is also an excellent catalyst for this reaction; however, the reaction takes a longer time for completion (Table 1, entry 6). Other Brønsted acids, such as acetic acid (Table 1, entry 8), 3,5-dinitrobenzoic acid (Table 1, entry 9), and (±)-1,1′-binaphthyl-2,2’-diyl hydrogen phosphate (Table 1, entry 10), were not effective for this transformation, and the starting material was recovered.

As shown in Table 2, the tandem Diels−Alder/aromatization reaction of **1a** is readily accomplished in a wide variety of solvents. Using TFA as the catalyst, we found that the reaction works well in halogenated solvents (entries 1−3), toluene (entry 4), or CH_3CN (entry 5) but less so in diethyl ether (entry 6) or

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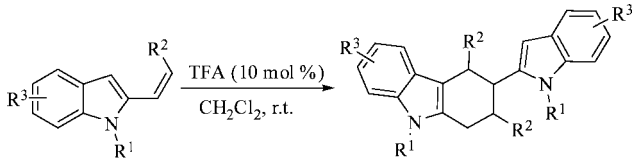
TABLE 3. Scope of TFA-Mediated Tandem Diels−Alder/Aromatization Reactions of 2-Vinylindoles[a]



1a-1s **2a-2s**

	substrate					
entry	R^1	R^2	R^3	product	time (min)	yield (%)[b]
1	Bn	H	H	**2a**	5	92
2	Bn	H	5-MeO	**2b**	10	83
3	Bn	H	5-Cl	**2c**	60	65
4	Bn	H	5-F	**2d**	15	84
5	Bn	H	5-Me	**2e**	30	85
6	Me	H	5-F	**2f**	120	93
7	Me	H	5-Cl	**2g**	90	68
8	Me	H	5-Br	**2h**	150	65
9	Me	H	H	**2i**	5	63
10	Me	H	5-MeO	**2j**	90	90
11[c]	Me	Me	5-MeO	**2k**	180	90
12[c]	Me	Me	H	**2l**	30	88
13[c]	Me	Me	5-Br	**2m**	540	69
14	allyl	H	H	**2n**	10	90
15[c]	allyl	Me	H	**2o**	10	82
16[c]	H	Me	H	**2p**	360	85
17	Bn	H	4-Cl-7-Me	**2q**	180	70
18	Bn	H	6-Cl-7-Me	**2r**	180	74
19[d]	Ts	H	5-MeO	**2s**	24 h	47

[a] Reaction conditions: vinylindole (0.25 mmol), TFA (0.025 mmol), CH_2Cl_2 (0.5 mL). [b] Isolated yield. [c] The diastereoselectivity of product was determined by ^{1}H NMR; see Supporting Information. [d] Ts: *p*-toluenesulfonyl.

tert-butyl methyl ether (entry 7). Highly polarized aprotic solvents such as DMF (entry 8) or polar protonic solvents such as MeOH and *i*-PrOH (entries 9 and 10) proved detrimental for this tandem sequence. As shown in entry 11, lower catalyst loading (10 mol %) was possible without significant loss in reaction efficiency. Further decreasing the catalyst loading to 5 mol % resulted in somewhat lower yield and extended reaction time (entry 12). Accordingly, the superior levels of reaction efficiency observed with 10 mol % of TFA in CH_2Cl_2 at room temperature (92% yield in 5 min) prompted us to select these reaction conditions for further exploration.

Experiments that probe the scope of the vinylindole component are summarized in Table 3. The reaction appears quite general with respect to the nature of the nitrogen substituents (R^1 = Bn, Me, allyl, *p*-toluenesulfonyl). This tandem process is also general with respect to indole architecture. Incorporation of alkyl and alkoxy substituents at the C(5)-indole position reveals that electronic modification of the indole ring can be accomplished with little influence on reaction yield (entries 2, 5, 10, and 11). Moreover, we have successfully utilized electron-deficient substrates in the context of 5-halogen-substituted vinylindoles (entries 3, 4, 6−8, and 13). Such halogenated 3-indolyl-substituted tetrahydrocarbazoles should be valuable synthons for further functional group transformation with the use of organometallic technologies.[13] The reaction appears quite tolerant with respect to the steric contribution of the olefin substituent of the substrate. Both terminal and internal vinyl-

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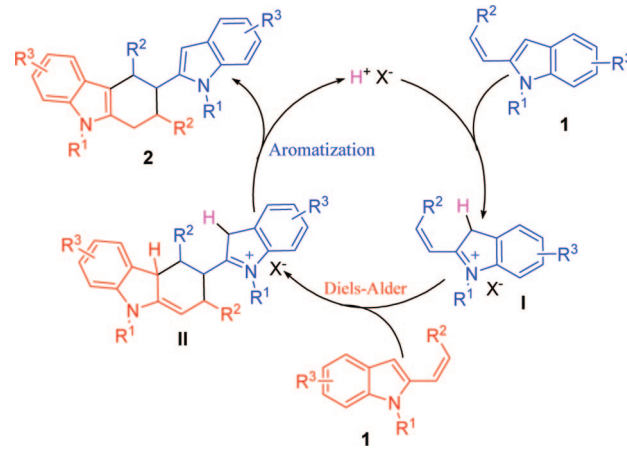
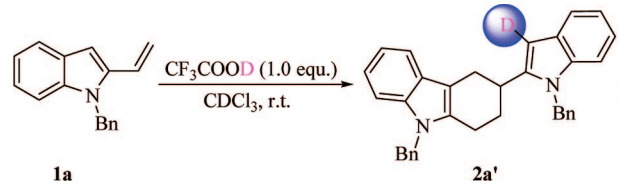
SCHEME 1. Possible Pathway for Brønsted Acid Mediated Tandem Diels−Alder/Aromatization Sequence



substituted indoles can readily participate in the reaction without significant loss in reaction efficiency (entries 8 vs 13, and 10 vs 11). Note that the internal vinyl indoles employed were isomeric mixtures and the reactions afforded the corresponding diastereoisomeric products. Perhaps more importantly, the 2-vinylindole without the protecting group on the nitrogen atom successfully underwent the cyclization to generate the expected product in 85% yield with great diastereoselectivity (entry 16). Furthermore, 2-vinylindoles bearing two substituents with different electronic properties were found to be quite reactive (entries 17 and 18). The structure of **2** was proposed by NMR and unambiguously confirmed by X-ray diffraction of **2e** as the representative.[14]

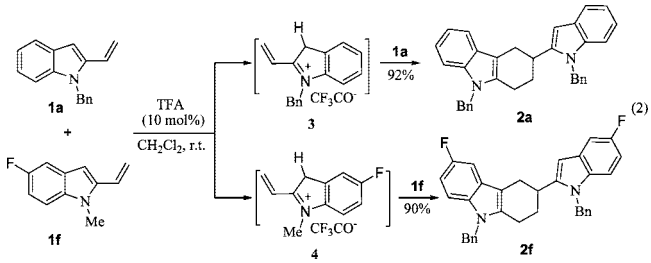
On the basis of these results, a possible pathway for the Brønsted acid mediated tandem Diels−Alder/aromatization reactions of 2-vinylindoles is outlined in Scheme 1. The protonation of the C(3)-position of the vinylindole (**1**) may generate an iminium intermediate **I**, which undergoes Diels−Alder reaction with another 2-vinylindole **1** to generate intermediate **II**. The subsequent aromatization of intermediate **II** would afford 3-indolyl-substituted tetrahydrocarbazole (**2**), with regeneration of the catalyst.[15]

To support this proposed mechanism, we have carried out D-labeling experiments. When 1.0 equiv of deuterated TFA was used in the reaction of **1a**, the corresponding deuterated product **2a′** was obtained in 90% isolated yield with almost 100% D incorporation at the 3′-position (eq 1).

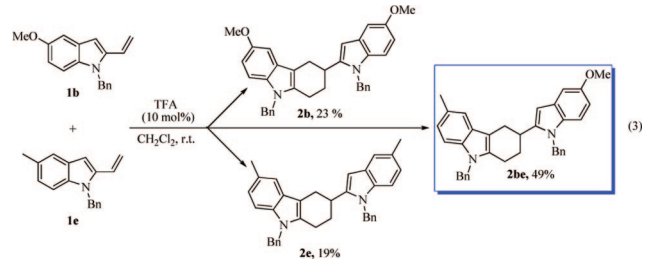


1a **2a'**

Furthermore, cross Diels−Alder/aromatization reactions of two different 2-vinylindole components were also performed. First, a relatively more active 2-vinylindole **1a** and a less active **1f** were subjected to the optimal reaction conditions. According to the above suggested mechanism, the protonation of more electron-enriched **1a** will be favorable to generate dienophile **3**. Subsequent Diels−Alder/aromatization with more active **1a** will result in the formation of **2a**. When substrate **1a** is totally consumed, the same reaction of **1f** will occur and afford product **2f** (eq 2).



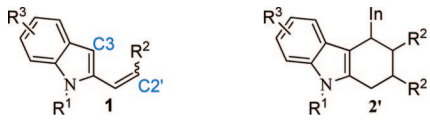
Then, an experiment of two vinylindoles with similar activity was carried out. As expected, a cross-product was indeed isolated in 49% isolated yield (eq 3).[14] These results are consistent with the proposed mechanism.



In summary, we have developed Brønsted acid catalyzed tandem Diels−Alder/aromatization reactions of 2-vinylindoles, which provide a highly concise route to the preparation of synthetically important tetrahydrocarbazole derivatives in good to excellent yields. The broad substrate scope, short reaction time, high yield, mild reaction conditions and operational simplicity make this protocol very useful and attractive.

(14) For the X-ray crystal structure of the representative compound **2e** and other details, please see Supporting Information.

(15) A possible product, **2′**, was not found in this reaction presumably because the nucleophilicity at the C3 position is greater than that at C2′ of the substrate **1**.



Experimental Section

General Procedure for the TFA-Catalyzed Diels−Alder/Aromatization. To a stirred solution of 2-vinylindole **1a** (58.3 mg, 0.25 mmol) in CH_2Cl_2 (0.5 mL) was added TFA (1.9 μL, 0.025 mmol) at room temperature, and the color of the mixture changed from colorless to dark purple immediately. After the reaction was completed (TLC), the reaction mixture was subjected to flash column chromatography on silica gel with petroleum ether/ethyl acetate (15:1) as eluent to obtain **2a** as a white solid (53.6 mg, 92%): mp 85−87 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.05−2.09 (m, 1H), 2.20 (d, J = 12.0 Hz, 1H), 2.64−2.74 (m, 2H), 2.94−2.98 (m, 1H), 3.13−3.19 (m, 2H), 5.24 (dd, J = 16.8, 23.4 Hz, 2H), 5.41 (s, 2H), 6.45 (s, 1H), 6.95 (d, J = 7.2 Hz, 2H), 6.99 (d, J = 7.2 Hz, 2H), 7.01−7.13 (m, 4H), 7.19−7.26 (m, 8H), 7.44 (d, J = 6.0 Hz, 1H), 7.59 (d, J = 6.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.9, 28.4, 29.7, 32.5, 46.2, 46.3, 98.2, 109.0, 109.5, 117.7, 119.0, 119.6, 120.0, 121.0, 125.7, 126.1, 127.2, 128.1, 128.7, 128.7, 134.8, 136.8, 137.0, 137.9, 138.0, 145.1. MS: m/z = 466.5. Anal. Calcd for $C_{34}H_{30}N_2$: C, 87.52; H, 6.48; N, 6.00. Found: C, 87.46; H, 6.39; N, 5.93.

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Supporting Information Available: Typical experimental procedures, spectroscopic details for all new compounds, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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