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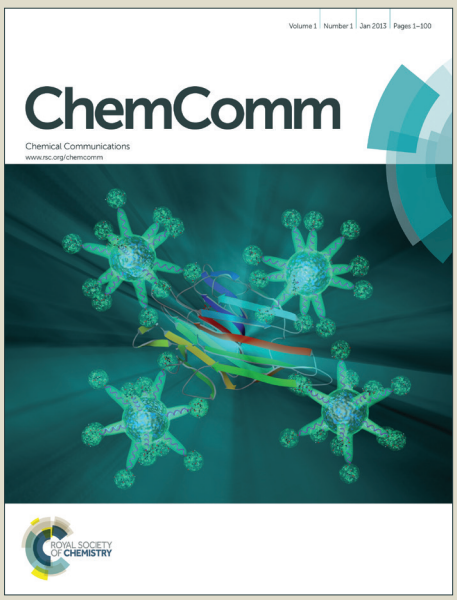

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Stereoselective Synthesis of 2,3-Disubstituted Indoline, Pyrrolidine and Cyclic Ether-Fused 1,2-Dihydroquinoline Derivatives using Alkyne Iminium Ion Cyclization of Vinylogous Carbamates: Switch of Regioselectivity using Internal Hydroxy Group as Nucleophile

Received 00th January 20xx
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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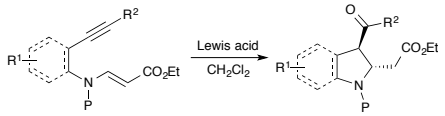
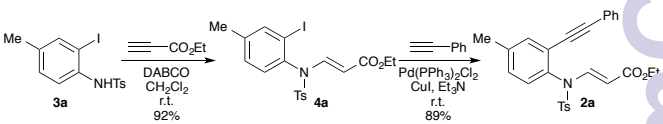
An intramolecular, alkyne iminium ion cyclization of vinylogous carbamates derived from *o*-alkynyl anilines and *N*-protected homopropargyl amines is developed for the stereoselective construction of *trans*-2,3-disubstituted indolines and pyrrolidine derivatives, respectively. Regioselectivity of the alkyne iminium ion cyclization could be switched using a hydroxy group as internal nucleophile resulting in cyclic ether-fused 1,2-dihydroquinolines. The entire process of nitrogen hetrocycle formation can also be carried out in a 'one-pot' manner starting from *o*-iodo aniline derivatives.

Indoline and pyrrolidine moieties are ubiquitous in biologically active synthetic and natural compounds.[1] As a result, diverse strategies have been developed for their synthesis.[2] An important method pioneered by Overman for the synthesis of nitrogen heterocycles is alkyne iminium cyclization. This approach involved intermolecular Mannich cyclization of an alkyne with formaldiminium ion in the presence of reactive external nucleophile.[3] Subsequent contributions from Speckamp and co-workers expanded the scope of this reaction many-fold by employing more reactive *N*-acyliminium ions.[4] Vinylogous carbamates are interesting push-pull functional groups, which have found use as excellent radical acceptors.[5] Vinylogous carbamates also serve as precursors of iminium ions in Pictet-Spengler and related reactions.[6] Interestingly, *trapping of iminium ions generated from vinylogous carbamates with alkynes as nucleophiles for the synthesis of nitrogen based heterocycles is conspicuous by its absence*. This is surprising as the products thus obtained will be effectively β-amino ester derivatives, which could be potentially valuable intermediates.[7] In a programme directed at using vinylogous carbonates and carbamates as precursors for the synthesis of oxa- and aza-cycles,[8] respectively, herein we disclose an alkyne iminium ion cyclization of vinylogous carbamates for the stereoselective synthesis of 2,3-disubstituted indoline and pyrrolidine derivatives. We further show that the regioselectivity of this cyclization can be switched by tethering the alkyne with an internal hydroxy group as nucleophile to give access to cyclic ether-fused 1,2-dihydroquinolines.



Scheme 1. Alkyne iminium ion cyclization on vinylogous carbamates for the synthesis of 2,3-disubstituted indolines and pyrrolidines.

Recently, we disclosed Lewis acid promoted generation of oxonium and iminium ions followed by their trapping with alkynes for the stereoselective construction of *trans*-2,3-disubstituted benzofurans and *N*-fused indole derivatives respectively.[9] Based on these studies, we envisioned that vinylogous carbamates prepared from *o*-alkynyl aniline derivatives could be good precursors for the synthesis of 2,3-disubstituted indoline derivatives. It was also proposed that, use of vinylogous carbamates of homopropargyl amines instead of aniline derivatives would give rise to substituted pyrrolidine derivatives (Scheme 1).



Scheme 2. Synthesis of *o*-alkynyl vinylogous carbamate precursor.

In order to test the hypothesis for construction of the indoline **1a**, synthesis of requisite vinylogous carbamate **2a** was initiated starting from the aniline derivative **3a**. Thus, reaction of ani

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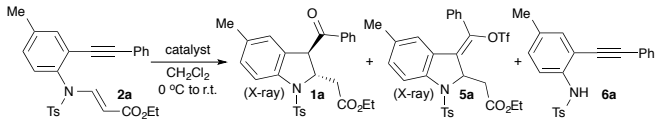
[b] † Electronic Supplementary Information (ESI) available: [Synthetic procedures and characterization data for all the new compounds. CCDC
[c] reference numbers 1408685 –1408690.]. See DOI: 10.1039/c000000x/
[d] DOI: 10.1039/x0xx00000x

derivative **3a** with ethyl propiolate in the presence of DABCO as the catalyst furnished the iodo vinylogous carbamate **4a**. Sonogashira coupling reaction of this iodide **4a** with phenylacetylene furnished the required precursor **1a** in good overall yield (Scheme 2).

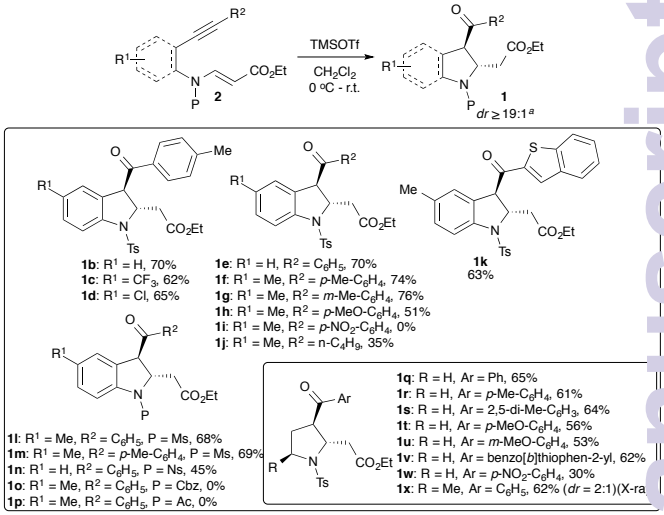
Table 1: Optimization of the alkyne iminium cyclization for the synthesis of 2,3-disubstituted indolines



Entry	Acid	Equiv.	Time (h)	Yield (%)[a] (**1a**/**5a**/**6a**)	*dr*[b]
1	CF_3SO_3H	1.1	3	64/7/0	(≥19:1)
2	CF_3SO_3H	2	3	54/12/0	(≥19:1)
3	**TMSOTf**	**1.1**	**3.5**	**73/0/0**	**(≥19:1)**
4	$In(OTf)_3$	1.1	12	63/9/5	(≥19:1)
5	$FeCl_3$	1.1	4	25/0/50	(≥19:1)
6	$BiBr_3$	1.1	4	16/0/64	(≥19:1)
7	$Cu(OTf)_2$	1.1	14	0/0/25[c]	-
8	$Bi(OTf)_3$	1.1	18	0/0/74[c]	-
9	$BF_3{\cdot}OEt_2$	1.1	24	-[d]	-
10	(±)-BPA	1.1	24	-[d]	-

[a]Isolated yield. [b]In all the cases, dr was determined on the crude reaction mixtures by ^{1}H NMR. [c]starting material recovered. [d]no reaction.

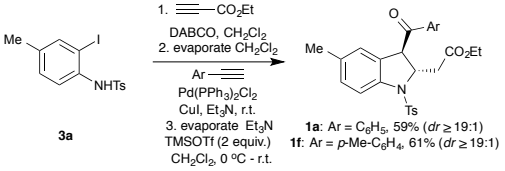
Attention was next turned towards studying the feasibility of alkyne iminium ion cyclization of vinylogous carbamate **2a** for the stereoselective synthesis of 2,3-disusbtituted indoline **1a** using various Lewis and Bronsted acids (Table 1). The reaction of vinylogous carbamate **2a** with CF_3SO_3H in CH_2Cl_2 at 0 °C gave *trans*-2,3-disubstituted indoline **1a** in good yield and excellent diastereoselectivity along with trace amount of vinyl triflate **5a** (Table 1, entry 1). Increasing the amount of acid used had little effect on the outcome of the reaction (Table 1, entry 2). When TMSOTf was used as the Lewis acid to effect this transformation, the reaction time was reduced, and indoline **1a** was obtained in 73% yield with excellent diastereoselectivity (Table 1, entry 3). When $In(OTf)_3$ was used as the catalyst, the required product **1a** was accompanied by small amounts of vinyl triflate **5a** and the hydrolysis product **6a** (Table 1, entry 4). Use of $FeCl_3$ and $BiBr_3$ as the catalyst resulted in poor yield of indoline **1a** (Table 1, entries 5 and 6). On the other hand, $Bi(OTf)_3$ and $Cu(OTf)_2$ were found to ineffective catalysts furnishing only hydrolyzed product **6a** (Table 1, entries 7 and 8). Interestingly, neither $BF_3{\cdot}OEt_2$ nor (±)-BINOL-phosphoric acid (BPA) could catalyze this transformation and unreacted starting material was recovered in both the cases (Table 1, entries 9 and 10). Based on these results, it was clear that TMSOTf was the catalyst of choice for further study. The structures of *trans*-2,3-disubstituted indoline **1a** and vinyl triflate **5a** were unambiguously ascertained by single crystal X-ray diffraction studies.[10]



Scheme 3. Scope of the alkyne iminium cyclization for the stereoselective synthesis of 2,3-disubstituted indoline and pyrrolidines. ([a]dr was determined on the crude reaction mixtures by ^{1}H NMR)

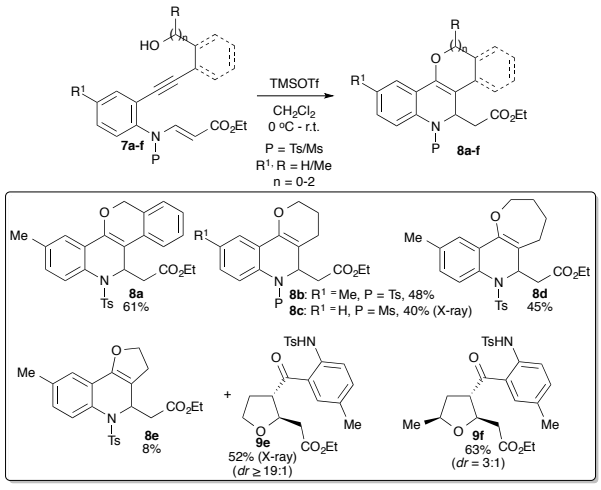
Attention was next turned towards studying the scope and limitations of this alkyne iminium ion cyclization. Vinylogous carbamate substrates bearing different substitutions in the two aryl rings were subjected to optimized reaction conditions and the results are summarized in the Scheme 3. Vinylogous carbamate **2b** (R^1 = H) having no substituent in the *para* position of nitrogen as well as **2c** (R^1 = CF_3) and **2d** (R^1 = Cl) having either mild or strong electron withdrawing group did not hamper the reaction and the corresponding indoline derivative **1b-d** were formed in good yields with excellent diastereoselectivity. Similarly, vinylogous carbamate **2e** having no substituent on both aryl rings worked well to give the indoline **1e**. It was observed that the substituent on the alkyne had definitive impact on the reactivity. Substrates **2f-h** bearing an electron releasing group participated in this reaction efficiently and gave the corresponding indolines **1f-h** in good yield. However, the substrate **2i** bearing an electron withdrawing nitro group failed to give the indoline **2i** and only hydrolysis of vinylogous carbamate was observed. Substrate **2j** bearing an alkyl substituent on the alkyne led to the formation of indoline **1j** in only moderate yield. Vinylogous carbamate **2k** bearing a heteroaromatic ring as substituent on the alkyne furnished the indoline **1k** in good yield and diastereoselectivity. We also explored the possibility of using other protecting groups on the nitrogen. Thus, vinylogous carbamates bearing other sulfonyl protecting groups such as mesyl (**2l-m**) and nosyl (**2n**) gave the corresponding indoline derivaties **1l-n**, respectively, in good yields and excellent diastereoselectivities. However, other *N*-protections such as Cbz (**2o**) and acetyl (**2p**) failed to give the corresponding indoline derivatives **1o-p**, rather only the hydrolyzed products **6o-p** were obtained. In all the cases, the stereochemistry of the major isomer was assigned on the basis of NOE experiments. We also explored the utility of this reaction for the synthesis of pyrrolidine derivatives. The reaction proved to be general with a variety of vinylogous carbamates bearing different aryl substituents on the alkyne moiety giving the *trans*-2,3-disubstituted pyrrolidines **1q-w** in good yields and excel

diastereoselectivity. It is pertinent to mention here that even *p*-nitrophenyl substituted alkyne derivative **2w** participated in the reaction and furnished the corresponding product **1w**, albeit in moderate yield. 2,3,5-trisubstituted pyrrolidine derivative **1x** too could be assembled using this protocol albeit with modest diastereoselectivity. The stereochemistry of the major diastereomer was confirmed by single crystal X-ray diffraction studies.[10] An interesting feature here is that the product **1x** is enantiomerically enriched as it is derived from (D)-alanine and could be potentially used in the target directed synthesis.



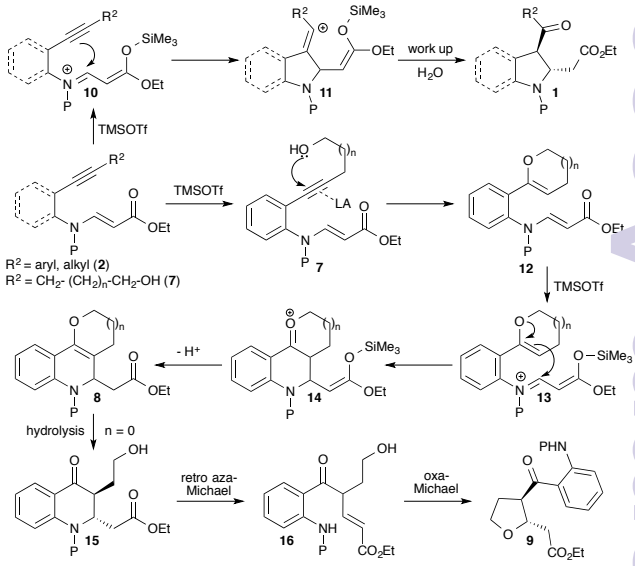
Scheme 4. 'One-pot' synthesis of 2,3-disubstituted indolines

It was thought that doing the entire sequence starting from aniline derivative **3a** in a 'one-pot' manner would be attractive as it would obviate the need of isolation of any intermediates. In order to check this, the *N*-protected aniline was treated with ethyl propiolate in the presence of DABCO in CH_2Cl_2. After complete consumption of the starting material, CH_2Cl_2 was evaporated, then arylalkynes were added sequentially along with $Pd(PPh_3)_2Cl_2$, CuI and Et_3N, and the mixture was stirred at rt for 6 hours. After evaporating Et_3N, CH_2Cl_2 and TMSOTf (2 equiv.) were added to the reaction mixture to furnish the indolines **1a** and **1f** in good overall yield and excellent diastereoselectivity (Scheme 4).



Scheme 5. Synthesis of dihydroquinolines by switch of regioselectivity. (*dr* was determined on the crude reaction mixtures by ^{1}H NMR)

At this juncture, we envisaged that if an appropriate nucleophile is tethered to the alkyne, it might trap the vinyl cation intermediate intramolecularly giving rise to another ring in the indoline derivative.[9b] One such nucleophile could be a hydroxy group, which is tethered to the alkyne. However, we also realized that the alkyne might actually participate in an intramolecular hydroalkoxylation in the presence of the Lewis acid prior to trapping the iminium ion intramolecularly. We argued that if such a step were to occur, it would indeed lead to a switch in the regioselectivity of attack of the alkyne and may actually result in the formation of a dihydroquinoline derivative. *While there are many reports on the transition metal catalyzed hydroalkoxylation of alkynes, metal-free variants of this reaction are uncommon.*[11] In order to test the feasibility of the proposed reaction; the alcohol **7a** was subjected to reaction with TMSOTf (Scheme 5). Interestingly, the reaction indeed furnished the isochromene-fused dihydroquinoline **8a** in good yield. Formation of the product **8a** is due to the hydroalkoxylation of alkyne in a *6-endo-dig* fashion resulting in the isochromene moiety followed by trapping of the iminium ion generated from vinylogous carbamate with the enol ether as the nucleophile (*vide infra*). In order to test the generality of the protocol, the alcohols **7b-c** were subjected to reaction with TMSOTf. The reaction indeed furnished the pyran-fused dihydroquinolines **8b** and **8c** in good yield.[10] When alcohol **7d** having an additional carbon in the tether was used in this cyclization, the oxepine-fused dihydroquinoline **8d** was obtained. On the other hand, when the alcohol **7e** having one carbon less in the tether was used, the dihydrofuran fused quinoline derivative **8e** was obtained in poor yields along with a rearranged product **9e**.[10] This reaction appeared to be general and when alcohol **7f** was subjected to Lewis acid treatment, the tetrahydrofuran **9f** was obtained in good yield and moderate diastereoselectivity as the major product and none of dihydroquinoline **8f** could be isolated.

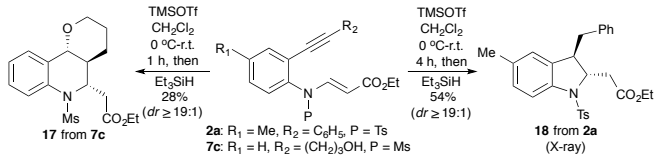


Scheme 6. Mechanism to explain the regioselectivity of the alkyne iminium ion cyclization and formation of the tetrahydrofurans **9e-f**

Formation of the indolines **1**, the switch in the regioselectivity of the alkyne iminium ion cyclization to give dihydroquinolines **8** as well as formation of the tetrahydrofuran products **9e-f** could be explained on the basis of the mechanism shown in Scheme 6. Vinylogous carbamate **2** gets activated with TMSOTf to generate the iminium ion **10**. Trapping of this iminium ion with the alkyne generates the vinyl cation **11**, which upon trapping with water during work-up leads to ketone **1** through the intermediacy of

corresponding enol form.[9a] On the other hand, in the case of vinylogous carbamate **7** bearing tethered hydroxyl group, the Lewis acid triggers a faster intramolecular hydroalkoxylation in a *endo-dig* fashion to generate cyclic enol ether **12**. In the subsequent step, the iminium ion **13** formed in the presence of Lewis acid is trapped by enol ether as nucleophile to give rise to the oxonium ion intermediate **14**, which upon loss of proton gives the cyclic ether fused dihydroquinoline derivative **8**. Formation of the tetrahydrofuran **9** can be explained by initial hydrolysis of enol ether to the keto alcohol **15**. The keto alcohol **15** undergoes a retro-aza-Michael reaction to enone **16**, which in turn generates the tetrahydrofuran **9** *via* an oxa-Michael addition.

Based on the mechanism, we argued that '*in situ*' trapping of the oxonium ion **14** with a nucleophile should be feasible and this would further the synthetic utility of this newly developed protocol. In order to test this hypothesis, the enyne **7c** was subjected to reaction with TMSOTf followed by addition of Et_3SiH (after complete consumption of starting material). The reaction indeed furnished the tetrahydropyran-fused dihydroquinoline **17** in moderate yield with excellent diastereoselectivity. Similar reaction with the alkyne **2a** gave the indoline **18** in good yield and diastereoselectivity (Scheme 7).[10]



Scheme 7. 'One-pot' alkyne iminium reductive cyclization.

In conclusion, we have developed a general strategy for the stereoselective synthesis of indoline and pyrrolidine derivatives using alkyne iminium ion cyclization. The regioselectivity of this cyclization could be switched using hydroxy group as internal nucleophile to furnish cyclic ether-fused dihydroquinoline. The synthesis of 2,3-disubstituted indolines and fused dihydroquinolines can also be carried out in a 'one-pot' manner using alkyne iminium ion reductive cyclization.

Acknowledgements

We thank DST and CSIR, New Delhi and BRNS, Mumbai for financial support. We thank Mr. Darshan Mhatre of the X-ray facility of the Department of Chemistry, IIT Bombay for collecting the crystallographic data. We are grateful to CSIR, New Delhi for the award of research fellowship to VP.

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