OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

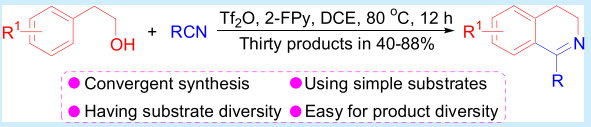
A Method for Bischler−Napieralski-Type Synthesis of 3,4-Dihydroisoquinolines

Lin Min, Weiguang Yang, Yunxiang Weng, Weiping Zheng, Xinyan Wang,* and Yuefei Hu*

Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing 100084, P.R. China

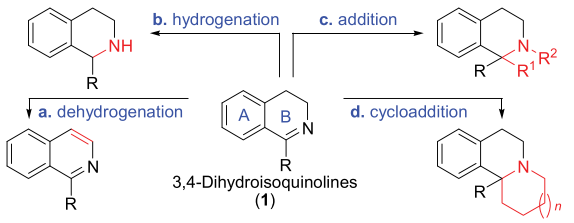
Supporting Information

ABSTRACT: A new method for the Bischler−Napieralski-type synthesis of 3,4-dihydroisoquinolines was developed by a Tf_2O-promoted tandem annulation from phenylethanols and nitriles. Its success was mainly due to the fact that a phenonium ion was formed in the process and practically functioned as a stable and reactive primary phenylethyl carbocation.



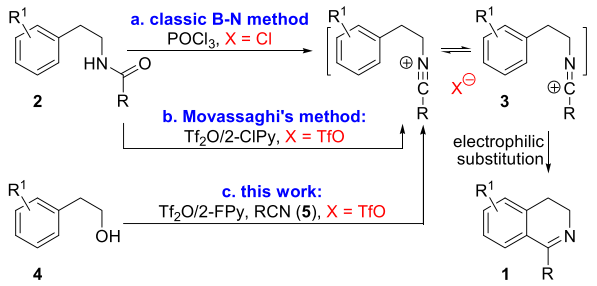
Due to the unique structure of 3,4-dihydroisoquinolines **1**, they have been broadly used as versatile synthons in organic synthesis. As shown in Scheme 1, their major transformations included (a) the dehydroaromatization of the B-ring,[1] (b) the hydrogenation of a double bond,[2] (c) the addition of a double bond,[3] and (d) the cycloaddition of a double bond.[4] Many 3,4-dihydroisoquinolines **1** have been used in the total synthesis of the bioactive natural alkaloids.[5]

Scheme 1. 3,4-Dihydroisoquinolines 1 as versatile synthons



Numerous methods for the synthesis of 3,4-dihydroisoquinolines **1** have been developed in the literature. The most prominent among them is the Bischler−Napieralski reaction (B−N reaction) for its practicability and reliability.[5,6] As shown in Scheme 2a, the B−N reaction is an intramolecular electrophilic aromatic substitution of *N*-arylethyl amides **2** to produce the products **1** in the presence of dehydrating agents. The mechanism studies for the B−N reaction proved that the *N*-arylethyl nitrilium salts **3** generated from the dehydration of the amides **2** were the key intermediates,[7] and their reactivity was influenced significantly by the counterions (X^-).[8] For example, the classic B−N reactions usually were limited to the amides **2** bearing the electron-rich arenes as substrates (Scheme 2a, R^1 = alkoxyl, dialkoxyl or trialkoxyl) by using $POCl_3$, P_2O_5, or $POCl_3$, etc. as dehydrating reagents.[6a] However, the high efficiency for the amides **2** bearing normal arenes (Scheme 2b, R^1 = H, Cl, or Br) was achieved in Movassaghi's work[9] when Tf_2O/2-ClPy was used as a dehydrating reagent. This advantage may result from the fact that the counterion TfO^- in their nitrilium salts **3** has almost no nucleophilicity.

Scheme 2. Classic and Modified B−N Methods



Although different dehydrating agents were employed in the classic B−N methods and Movassaghi's method, they actually used common substrates and pathways. From a synthetic point of view, all these methods belong to linear synthesis. As a result, their common substrates *N*-arylethyl amides **2** bearing the same carbon numbers and functional groups as the target products **1** must be premade by a multistep synthesis.[10] Herein, we report a new method for the synthesis of 3,4-dihydroisoquinolines **1** via a Tf_2O-promoted tandem annulation from phenylethanols **4** and nitriles **5**. As shown in Scheme 2c, this method can be considered as a modified B−N reaction because its key steps involve the formation and the electrophilic aromatic substitutions of the nitrilium salts **3**. However, this method was carried out through a convergent synthesis and the use of easy substrates.

Investigation indicated that, like the dehydration of amides, the *N*-alkylation of nitriles with carbocations is also an efficient method for the formation of nitrilium salts.[8] But this method has not been efficiently used for the synthesis of 3,4-dihydroisoquinolines **1** thus far in the literature. For example, Lora-Tamayo[11]

Received: February 11, 2019

DOI: 10.1021/acs.orglett.9b00534
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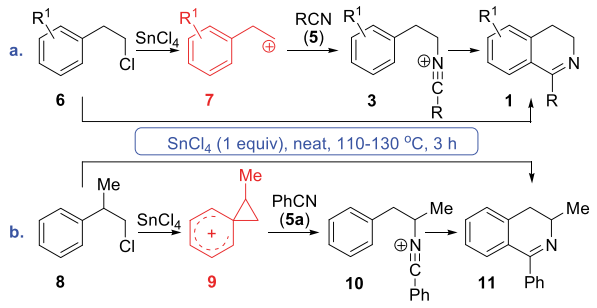
et al. in 1960 reported a synthesis of 3,4-dihydroisoquinolines **1** via a $SnCl_4$-promoted cyclization of 2-phenylethyl chlorides **6** and nitriles **5**. As shown in Scheme 3a, they proposed that a

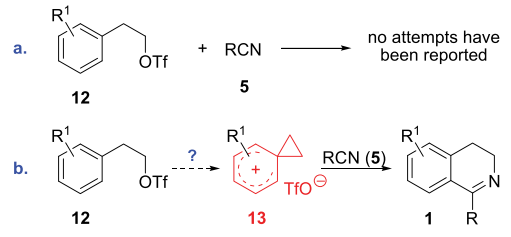
Scheme 3. Lora-Tamayo's Method and Ho's Method



primary phenylethyl carbocation **7** was formed by a normal ionization of **6** and then quickly underwent an *N*-alkylation with nitrile **5** to give an *N*-phenylethyl nitrilium salt **3**. However, this method has rarely been used in past decades[12] due to its hash conditions. However, Ho[13] et al. in 2003 reported that 2-methyl-2-phenylethyl chloride (**8**) reacted with benzonitrile (**5a**) under Lora-Tamayo's conditions to yield 1-phenyl-3-methyl-3,4-dihydroisoquinoline (**11**) (Scheme 3b). They proved that the migration of the methyl group in this reaction resulted from the formation of a stable phenonium ion **9**, which was the real reactive intermediate rather than the unstable primary carbocation. In literature, the phenonium ions have been well studied,[14] and they functioned as stable and reactive primary phenylethyl carbocations driven by the relief of the cyclopropyl ring strain and recovery of the aromatic benene.[15]

In another example, the *N*-alkylation of nitriles with alkyl triflates has often been used for the formation of nitrilium salts.[8] However, this method is usually limited to the formation of *N*-methylnitrilium salts (RC≡N$^+$−Me) by using methyl triflate (MeOTf) as an alkylating reagent.[16] This result may be caused by the fact that the carbocations formed from the alkyl triflates bearing a carbon chain longer than two carbons may easily carry out the undesired carbocation rearrangements during the *N*-alkylations. As a result, 2-phenylethyl triflates **12** have been never used to react with nitriles **5** for the synthesis of 3,4-dihydroisoquinolines **1**, even though some of them were known products[17] (Scheme 4a). However, all the above investigations

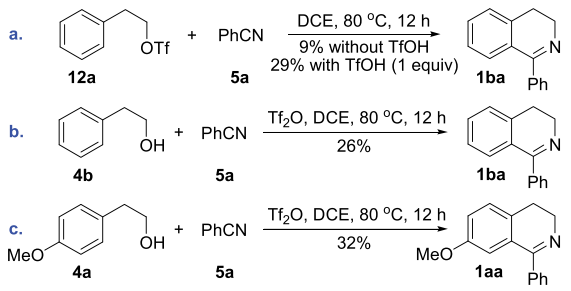
Scheme 4. Hypothesis for the Synthesis of 1 from 12



enabled us to realize that the carbocations generated from 2-phenylethyl triflates **12** may be stabilized by forming the corresponding phenonium ions **13**, which then react with nitriles **5** to yield 3,4-dihydroisoquinolines **1** (Scheme 4b).

Thus, the mixture of phenylethyl triflate (**12a**) and benzonitrile (**5a**) in DCE was heated at 80 °C for 12 h. As shown in Scheme 5a, the desired product 1-phenyl-3,4-dihydroisoquinoline (**1ba**) was obtained only in 9% yield. To

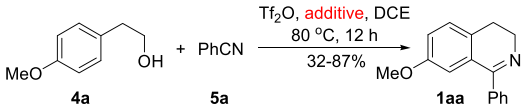
Scheme 5. Primary Conditional Tests



our surprise, **1ba** was obtained in 26% yield by using the phenylethyl triflate (**12a**) generated in situ from phenylethanol (**4b**) and Tf_2O (Scheme 5b). This result suggested that the conversion of triflate **12a** into its phenonium ion **13a** may be catalyzed by TfOH released from the triflation of **4b**.[18] This phenomenon was confirmed by the fact that the yield of **1ba** was tripled (29%) when 1 equiv of TfOH was employed in Scheme 5a. As was expected, 7-methoxy-3,4-dihydroisoquinoline (**1aa**) was obtained in 32% yield when electron-rich 4-methoxyphenylethanol (**4a**) was used as a substrate (Scheme 5c).

Thus, the conditions for the synthesis of **1aa** were optimized as shown in Table 1. The ratios of **4a** to **5a** (entries 1−4) showed

Table 1. Effects of the Substrates and Additives[a]



entry	**4a**/**5a** (mole)	additive	**1aa**[b] (%)
1	1:1		32
2	1:1.2		50
3	1:1.5		56
4	1.5:1		33
5	1:1.5	DABCO	70
6	1:1.5	Et_3N	75
7	1:1.5	DBU	80
8	1:1.5	DAMP	84
9	**1:1.5**	**2-FPy**	**87**
10	1:1.5	2-ClPy	85
11	1:1.5	2-IPy	85
12	1:1.5	2,6-Cl_2Py	75

[a]The mixture of **4a** and **5a** in DCE (3 mL) was treated with Tf_2O (2 mmol) at 0 °C for 30 min with or without an additive (1 mmol) and then was heated at 80 °C for 12 h. [b]Isolated yields.

significant influences to the results, and the best result was obtained at 1:1.5 (entry 3). In order to modulate the strength of TfOH, several amine-based additives were tested as acid-binding agents. As shown in entries 5−7, the yield of **1aa** was significantly improved by adding DABCO, Et_3N, or DBU. The pyridine derivatives seemed to be better additives to give higher yield of **1aa** (entries 8−12). Finally, the conditions in entry 9 were chosen for further conditional tests.

As shown in Table 2, the yield of **1aa** was decreased by increasing or decreasing the reaction temperatures (entries 2 and 3). The yield of **1aa** was decreased by reducing the reaction

DOI: 10.1021/acs.orglett.9b00534
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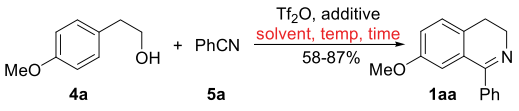
Table 2. Effects of the Temperature, Time, and Solvent[a]



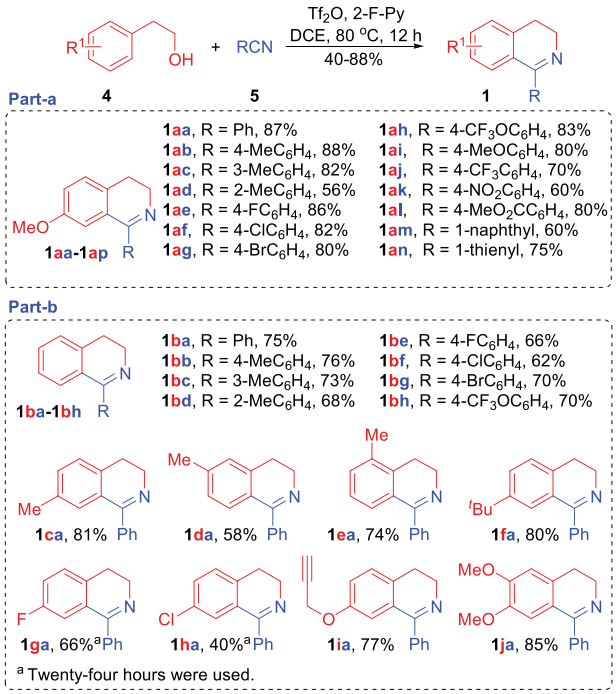
entry	temp (°C)	time (h)	solvent	1aa[b] (%)
1	**80**	**12**	**DCE**	**87**
2	70	12	DCE	58
3	90	12	DCE	86
4	80	10	DCE	74
5	80	14	DCE	87
6	80	12	toluene	65
7	80	12	$CHCl_3$	63

[a]The mixture of **4a** (1 mmol), **5a** (1.5 mmol), and 2-FPy (1 mmol) in DCE (3 mL) was treated by Tf_2O (2 mmol) at 0 °C for 30 min and then was heated at the given temperatures and times. [b]Isolated yields.

time, but no improvement was observed by extending the reaction time (entries 4 and 5). Compared to DCE, PhMe and $CHCl_3$ were quite poor solvents for this method (entries 6 and 7). Finally, the conditions in entry 1 were assigned as the standard conditions.

At this time, we realized that we had found a new method for an efficient synthesis of 3,4-dihydroisoquinolines **1**. To the best of our knowledge, no such method has been reported in literature so far. Thus, the scope of this method was tested under standard conditions. As shown in part a of Scheme 6, 4-methoxyphenylethanol (**4a**) reacted smoothly with different nitriles **5a**–**n** to yield the corresponding products **1aa**–**an**. In these transformations, the steric and electronic effects of nitriles were observed clearly. For example, **1aa** was obtained in 88% yield from *p*-methylbenzonitrile (**5a**), while **1ad** was obtained in only 56% yield from *o*-methylbenzonitrile (**5d**). As was expected, **1aj** (70%) and **1ak** (60%) were synthesized in relatively lower yields from the electron-withdrawing-group substituted 4-trifluoromethylbenzonitrile (**4j**) and 4-nitrobenzonitrile (**4k**), respectively.

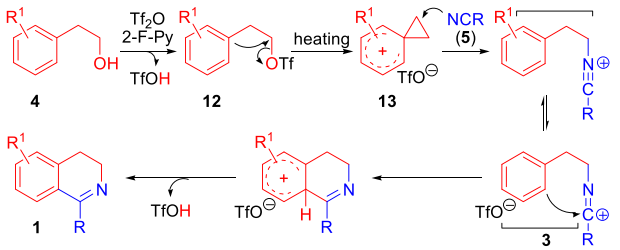
Scheme 6. Scope of the Substrates and the Products



As shown in part b of Scheme 6, like Movassaghi's method, the non-electron-rich phenylethanol (**4b**) reacted with nitriles **5a**–**h** to give the corresponding products **1ba**–**bh** in satisfactory yields under standard conditions. Due to the electronic effects, the product **1da** was synthesized from *m*-methylphenylethanol (**4d**) in a lower yield (58%) compared to the products **1ca** (81%) and **1ea** (74%). By prolonging the reaction time, the halogen-substituted phenylethanols **4g** and **4h** were successfully converted into the corresponding products **1ga** and **1ha**. To our surprise, the product **1ia** was synthesized smoothly, and its terminal alkyne stayed under these conditions. Under standard conditions, the products **1aa** and **1ba** were prepared on 2 g scales in 82% and 68% yields, respectively.

However, the phenylethanols bearing strong electron-withdrawing-groups, such as acyl, cyano, or nitro groups, were not suitable substrates for this method. Complicated mixtures were obtained when benzyl alcohol ($PhCH_2OH$) or 3-phenyl-1-propanol [$Ph(CH_2)_3OH$] were used as a substrate to react with **5a**, possibly because they could not form the phenonium ions. Thus, a possible pathway was proposed for our new method. As shown in Scheme 7, phenylethanol **4** initially was triflated by Tf_2O to form phenylethyl triflate **12**. Promoted by TfOH and heating, the triflate **12** lost its triflate group to give the phenonium ion **13**. Then the nitrile **5** was *N*-alkylated by phenonium ion **13** to produce a reactive intermediate nitrilium salt **3**. Finally, nitrilium salt **3** undergent an intramolecular electrophilic aromatic substitution to give the target product 3,4-dihydroisoquinoline **1**.

Scheme 7. Proposed Pathway for the Formation of 1



To confirm that the phenonium ion **13** is the active intermediate for our method, three controlled experiments were made under the standard conditions. As was expected, 3,3- and 4,4-dideuterio products (**15** and **16**) were obtained as 1:1 mixture in 61% yield when 1,1-dideuterio-2-phenylethanol (**14**) was employed as a substrate (Scheme 8a). 1-Phenyl-3-methyl-3,4-dihydroisoquinoline (**11**) was obtained as single product when 2-methyl- or 1-methyl-2-phenylethanol (**17** or **18**) was employed as a substrate (Scheme 8b,c). The migration of the deuterium and the methyl group in Scheme 8a,b indicated that the phenonium ion **13** is indeed the active intermediate for our method. The low yields of product **11** in Schemes 8b,c may be caused by the fact that the corresponding nitrilium ion (the analogues of **3**) was subjected to a retro-Ritter reaction. This phenomenon was fully in agreement with the early studies of the B–N reaction where the nitrilium ion with a more substituted carbon bonded to the *N*-atom has more tendency to undergo a retro-Ritter reaction.[7a,19] In fact, this is also the reason why the B–N reaction is mainly used for the synthesis of 3,4-nonsubstituted 3,4-dihydroisoquinolines.[5,6,9]

DOI: 10.1021/acs.orglett.9b00534
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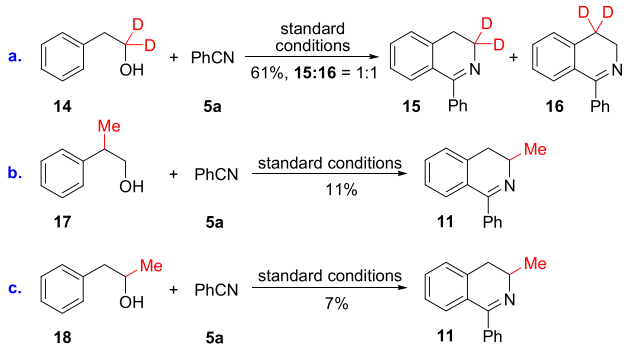
Scheme 8. Three Controlled Experiments and Results



In conclusion, a new method for the Bischler−Napieralski-type synthesis of 3,4-dihydroisoquinolines was developed by a Tf_2O-promoted tandem annulation from phenylethanols and nitriles. Its success is mainly due to the formation of the stable phenonium ions, by which the *N*-alkylation of nitriles was achieved efficiently to give the key intermediate *N*-phenylethyl nitrilium triflate. The method has two distinctive advantages: (a) it changes the Bischler−Napieralski reaction from a linear synthesis into a convergent synthesis and (b) it changes the substrates from *N*-phenylethyl amides into phenylethanols. Since both advantages practically promote the substrate and product diversities of the Bischler−Napieralski reaction, we may expect that this method will have widespread applications in organic synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00534.

Experiments, characterization, and ^1H and ^{13}C NMR spectra for all products **1aa-1an**, **1ba-1bh**, **1ca-1ja**, **11**, **14**, and the mixture of **15**/**16** (1:1) (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: yfh@mail.tsinghua.edu.cn.
*E-mail: wangxinyan@mail.tsinghua.edu.cn.

ORCID

Xinyan Wang: 0000-0002-7030-0418

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (Nos. 21472107 and 21372142).

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DOI: 10.1021/acs.orglett.9b00534
Org. Lett. XXXX, XXX, XXX−XXX