Chinese Chemical Letters 31 (2020) 729–732

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Communication

Synthesis of tetrahydroisoquinolines through $TiCl_4$-mediated cyclization and Et_3SiH reduction

Zeyu Shi[a], Qiong Xiao[a,b,*], Dali Yin[a,b]

[a] State Key Laboratory of Bioactive Substances and Functions of Natural Medicines, Institute of Materia Medica, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing 100050, China
[b] Department of Medicinal Chemistry, Beijing Key Laboratory of Active Substances Discovery and Drugability Evaluation, Institute of Materia Medica, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing 100050, China

ARTICLE INFO

Article history:
Received 27 July 2019
Received in revised form 4 September 2019
Accepted 11 September 2019
Available online 12 September 2019

Keywords:
Tetrahydroisoquinoline
$TiCl_4$
Cyclization
Et_3SiH
Telescoped reaction

ABSTRACT

A versatile and efficient telescoped reaction sequence for the synthesis of tetrahydroisoquinolines (THIQs) is reported that uses $TiCl_4$ to promote cyclization of a benzylaminoacetal derivative and Et_3SiH for reduction of the intermediate 4-hydroxy-THIQ. This method is complimentary to the classical Pomeranz-Fritsch and related reactions since it tolerates electron-withdrawing substituents and allows access to 8-substituted THIQs.

Tetrahydroisoquinoline (THIQ) is an important structural motif found in many alkaloid natural products [1] and several drugs including nomifensine [2], hydrastinine [3], dehydroemetine [4] and ecteinascidin 743 [5]. Beyond the classic Pictet-Spengler reaction and selective hydrogenation of isoquinolines, there are few reactions that can be used to synthesize THIQ conveniently [6]. The Pictet-Spengler reaction (Scheme 1) involves condensation of phenethylamines with an aldehyde or ketone to form an intermediate iminium ion that undergoes ring closure by electrophilic aromatic substitution, which limits the substrate scope to electron-rich aromatic systems. A Br ønsted acid catalyst in protic solvent is typically employed with heating thereby restricting the chemoselectivity. Because of the mechanism, meta-substituted phenethylamine analogues tend to afford 6-substituted THIQ over the 8-substituted THIQ regioisomers [7]. The related Bischler-Napieralski and Pictet-Gams cyclization of phenylethylamides suffer from these same limitations. Complimentary to the above methods, the Pomeranz-Fritsch reaction is another strategy for the preparation of isoquinolines, especially 8-substituted THIQs. The reaction involves the acid-promoted condensation of a benzaldehyde with a 2,2-dialkoxyethylamine, but is also restricted to electron-rich benzaldehyde derivatives. Besides, other synthesis routes of THIQ derivatives such as visible-light-promoted transition-metal-free approach [8] and silver-catalyzed radical cascade cyclization have been reported [9].

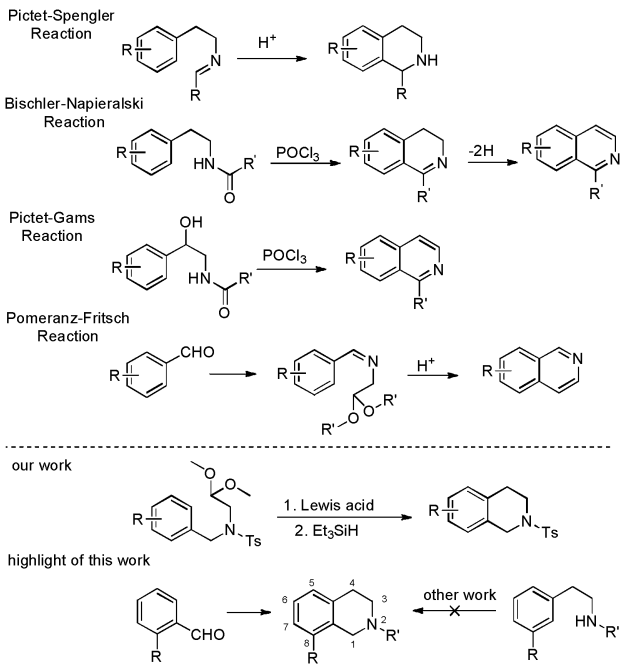
Here, we describe the serendipitous discovery of a one-pot route for the synthesis of THIQs *via* $TiCl_4$ mediated ring-closure of benzylaminoacetal derivatives (Table 1).

Our initial goal was to synthesize THIQ analogue **1f** through a Jackson-modifed Pomerantz-Fritsch reaction of **1a** to afford **1b** followed by hydrogenation [10]. Unfortunately, the desired product **1b** was not observed using 6 mol/L aqueous HCl in dioxane and only **1c** arising from acetal hydrolysis under the aqueous conditions was obtained in 85% yield. We next explored non-aqueous condition employing the Lewis acid $AlCl_3$ in dichloromethane (DCM) and were heartened to observe **1b** about 10% yield (just LC–MS confirmed).

Subsequently, we screened several Lewis acids to promote the cyclization of **1a** to **1b** including $BF_3{\cdot}OEt_2$ [11], $Bi(OTf)_3$, $InCl_3$ and $Al(OTf)_3$ in DCM at room temperature, but all exclusively furnished **1c** (Table 1, entries 3–6). The substrate **1a** decomposed with Eaton's reagent (Table 1, entry 7) and there was no reaction with SmI_2 (Table 1, entry 8). To our surprise, treatment of **1a** with $TiCl_4$ in DCM at room temperature afforded 7-bromo-8-methoxy-2-tosyl-1,2,3,4-tetrahydroisoquinolin-4-ol (**1d**) in an impressive 85% yield (Table 1, entry 9). Based on our previous experience with reduction of benzyl ketones and alcohols with $TiCl_4/Et_3SiH$, we hypothesized

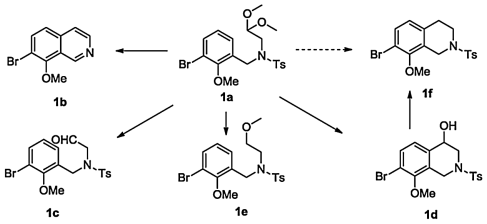
* Corresponding author at: State Key Laboratory of Bioactive Substances and Functions of Natural Medicines, Institute of Materia Medica, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing, 100050, China.
E-mail address: xiaoqiong@imm.ac.cn (Q. Xiao).

https://doi.org/10.1016/j.cclet.2019.09.023



Scheme 1. Methods for synthesis of THIQs and isoquinolines.

Table 1
Selected results for screening the reaction conditions.[a]



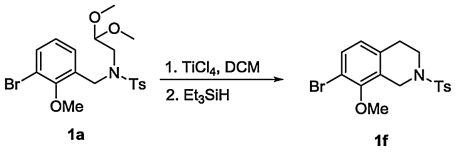
Entry	Acid	Additive (equiv.)	Solvent	Product	Yield (%)[b]
1	HCl (6 mol/L)	NA	1,4-dioxane	**1c**	85
2	$AlCl_3$	NA	DCM	**1b**	10
3	$Bi(OTf)_3$	NA	DCM	**1c**	66
4	$BF_3{\cdot}OEt_2$	NA	DCM	**1c**	70
5	$InCl_3$	NA	DCM	**1c**	32
6	$Al(OTf)_3$	NA	DCM	**1c**	74
7	Eaton's Reagent[c]	NA	DCM	dc[f]	
8	SmI_2	NA	DCM	NR[g]	
9	$TiCl_4$	NA	DCM	**1d**	85
10[d]	$TiCl_4$	Et_3SiH (1.5)	DCM	**1e**	75
11[e]	$TiCl_4$	Et_3SiH (1.5)	DCM	**1f**	34

[a] Reaction conditions: The reactions were carried out with **1a** (1.0 mmol), acid (1.5 mmol), additive (1.5 mmol) and solvent (2.0 mL) for 6 h at room temperature.
[b] Isolated yield.
[c] 7.7 wt% phosphorus pentoxide solution in methanesulfonic acid.
[d] Et_3SiH was added immediately after $TiCl_4$.
[e] Et_3SiH was added 3 h after $TiCl_4$.
[f] dc: decomposed.
[g] NR: no reaction.

addition of Et_3SiH to the reaction mixture would directly afford the desired THIQ **1f** [12]. We thus treated **1a** with $TiCl_4$ and Et_3SiH in one pot, but observed only the formation of **1e** (Table 1, entry 10). This results clearly indicates reduction proceeds faster than cyclization. We then tried a telescoping synthesis by the addition of $TiCl_4$ to **1a** in DCM followed by Et_3SiH (1.5 mmol) after 3 h without any work-up and obtained **1f** in 34% yield (Table 1, entry 11).

Encouraged by this result, we optimized conditions to obtain more satisfactory results (Table 2). To improve the applicability of

Table 2
Optimization of reaction conditions.[a]

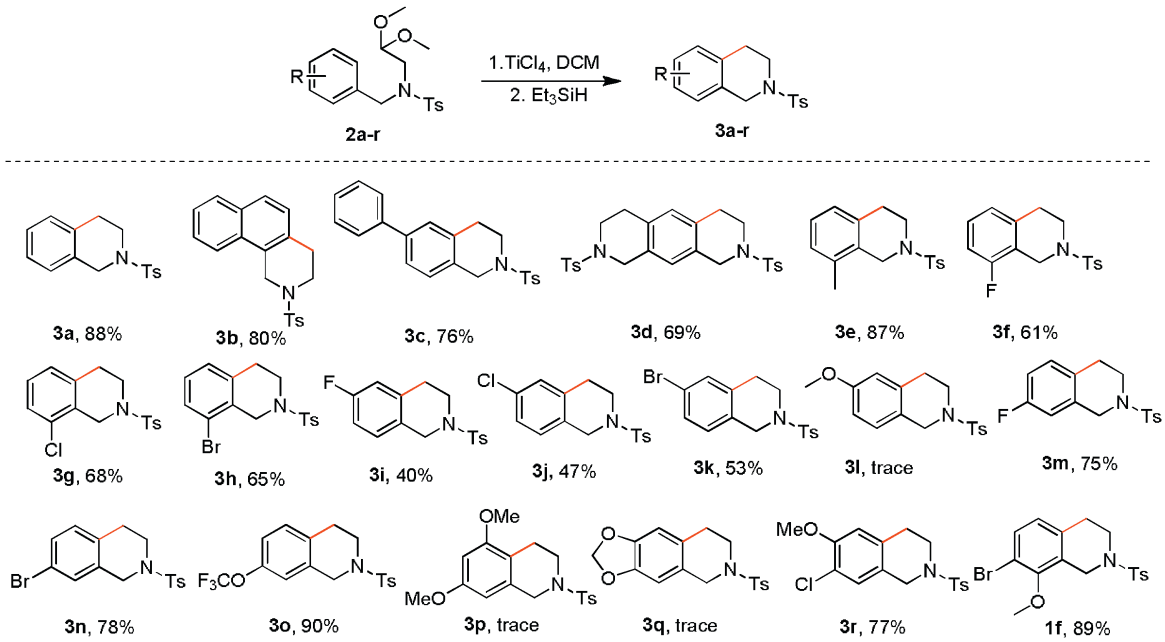


Entry	**1a**/$TiCl_4$/Et_3SiH	Time (h) (step 1)	Time (h) (step 2)	Yield (%)[b]
1	1:1:1	3	6	ND[c]
2	1:2:2	3	6	53
3	1:4:4	3	6	74
4	1:2:2	3	12	69
5	1:4:4	3	12	89
6	1:2:2	6	6	48
7[d]	1:2:2	3	6	42
8[e]	1:2:2	3	6	NR

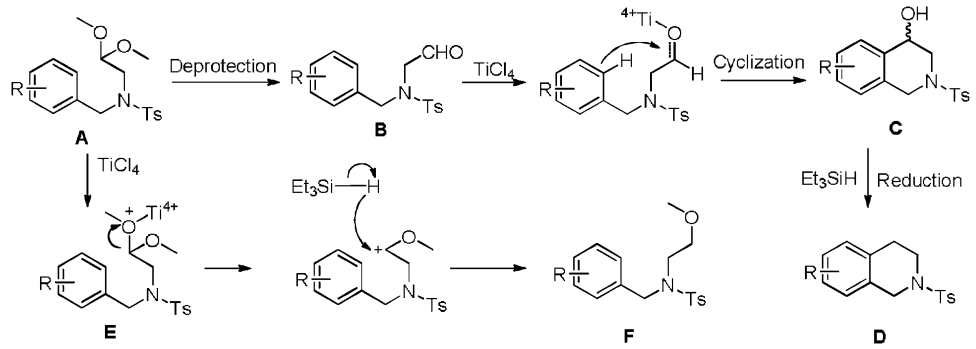
[a] Reaction conditions: The reactions were carried out with **1a**, $TiCl_4$ in DCM (5 mL) for the indicated times, then Et_3SiH was added.
[b] Isolated yield.
[c] **1d** is the only product.
[d] Reflux.
[e] MeCN as solvent.

the reaction, we examined other parameters including the ratio of reagents and the reaction time for each step. 1 equiv. of $TiCl_4$ and Et_3SiH produced only **1d** instead of **1f** (Table 2, entry 1). Increasing the amounts of $TiCl_4$ and Et_3SiH was necessary to promote the reaction, 2 equiv. of $TiCl_4$/Et_3SiH affording **1f** in 53% yield, while 4 equiv. gave **1f** in 74% yield (Table 2, entries 2 and 3). Prolonging the reaction time in step 2 from 6 h to 12 h led to higher yields, whereas increasing the reaction time of step one from 3 h to 6 h slightly diminished the yield (Table 2, entries 4–6). We explored other solvents (MeCN) as well as heating the reaction at reflux, but both modifications to the reaction conditions were deleterious (Table 2, entries 7 and 8). We also tried different *N*-protecting group such as *N*-acetyl, *N*-trifluoroacetyl and naked NH compounds as substrates. Unfortunately, only Ts group in the $TiCl_4$ in DCM conditions works to afford corresponding product. Therefore, in this work Ts may be the most suitable group protects the N-atom.

With the optimized reaction conditions (Table 2, entry 5), we examined the scope and limitation of this two-step, one-pot reaction for the synthesis of THIQs. As shown in Scheme 2, most of substrates (**2a-r**) afforded the desired products in good-to-excellent yields. To our delight, electron-withdrawing substituents were well tolerated with analogues substituted at the *meta*-position (**3m** and **3n**) affording the highest overall yield followed in relative order by the *ortho*-position (**3f-h**) and *para*-position (**3i-k**). Exceeding our expectations, the *meta*-substituted substrates reacted with high regioselectivity to afford **3m-o**. A clear limitation to the method is substrates bearing monomethoxy (**2i**) or dimethoxy (**2p** and **2q**) groups, which did not react. It is noteworthy that introduction of an adjacent halogen substituent next to the alkoxy in **1a** and **2 r** or replacement of the methyl ether with a trifluoromethyl ether in **2o** provided **1f**, **3r** and **3o** in the highest overall yields. The procedure for the synthesis and spectra data were shown in Supporting information. In these cases, substrates with strong electron-withdraw groups, such as $-NO_2$, $-CF_3$ could not react. Electron-donating group like -Me can afford the product with high yield. However, both mono-methoxy and dimethoxy compounds did not give products. We speculated that the lone pair electron of methoxy oxygen may coordinate with $TiCl_4$ to form a strong electro-withdrawing effect, thereby deactivating the aromatic system. When a bromo- or chloro-substituent is inserted next to MeO-, it blockades the formation of



Scheme 2. Substrate scope with variation of THIQ. All reactions were carried out with **1a** (1.0 mmol), $TiCl_4$ (4.0 mmol) in DCM (5 mL) at room temperature for 3 h followed by the addition of Et_3SiH (4.0 mmol) and stirring for another 12 h. Isolated yield.



Scheme 3. The plausible mechanism.

the methoxy-$TiCl_4$ complex, thus the reaction works again. The advantage of this method could be used with weak electron-withdrawing group like halogens and -OCF_3.

To explore the reaction process on a larger scale, we attempted the gram scale synthesis of **1f**. We added $TiCl_4$ (6.4 mL) in **1a** (13.4 g) with 100 mL of DCM. Here control of the reaction temperature during the addition of $TiCl_4$ was critical to prevent a large exotherm that compromised the yield and led to multiple byproducts. This was accomplished by slow addition and pre-cooling the reaction to −10 °C. Finally, afforded 9.8 g **1f** in 85% yield.

Actually, the proposed mechanism was basically disclosed when we screened the reaction condition. Scheme 3 describes the mechanism for the formation of compounds **D** and **F** from acetal **A**. Initially, acetal **A** is deprotected to furnish intermediate aldehyde **B** which can be isolated. In the absence of Et_3SiH, **B** cyclizes to produce tetrahydroisoquinolin-4-ol **C** by $TiCl_4$, which can also be isolated as the only product, but undergoes *in situ* reduction by Et_3SiH to afford **D** in a telescoped reaction sequence. Compound **D** can be afforded from intermediate **B** and **C**. On the other hand, when the Et_3SiH and $TiCl_4$ are introduced simultaneously, the silane reacts directly with the oxocarbenium intermediate **E** to generate the undesired reduction product **F**.

In conclusion, we have reported a mild and efficient method for the preparation of THIQs from benzylaminoacetal derivatives. The method employs $TiCl_4$ to promote acetal deprotection and subsequent cyclization in DCM at room temperature, thereby avoiding high temperature as well as the strong Br ønsted acid employed in the traditional Pomeranz-Fritsch reaction. The telescoped reaction sequence uses Et_3SiH in a second step to reduce the intermediate hydroxyl-THIQ to directly afford a THIQ. The method is noteworthy for its wide-substrate tolerance, accommodation of electron-withdrawing substituents in the aryl ring, and ability to give 8-substituent THIQs products that are not easily accessed by conventional approaches to THIQs. The combination of $TiCl_4$/Et_3SiH provides a useful and complementary method for the synthesis of valuable THIQ products from simple benzaldehyde derivatives.

Acknowledgments

We are grateful for financial support from Drug Innovation Major Project (No. 2018ZX09711-001-005) and CAMS Collaborative Innovation Project (No. 2017-I2M-2-004).

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cclet.2019.09.023.

References

[1] (a) J.D. Scott, R.M. Williams, Chem. Rev. 102 (2002) 1669–1730;
(b) Y. Kashiwasa, A. Aoshima, Y. Ikeshiro, et al., Bioorg. Med. Chem. 13 (2005) 443–448.
[2] (a) A.D. Pechulis, J.P. Beck, M.A. Curry, et al., Bioorg. Med. Chem. Lett. 22 (2012) 7219–7222;
(b) W.O. Shekim, A. Masterson, D.P. Cantwell, et al., J. Nerv. Ment. Dis. 177 (1989) 296–299;
(c) E. Zara-Kaczian, L. Gyorgy, G. Deak, et al., J. Med. Chem. 29 (1986) 1189–1195.
[3] R.W. Freudenmann, F. Oxler, S. Bernschneider-Reif, Addiction 101 (2006) 1241–1245.
[4] G.H. Al-Khateeb, T.I. Al-Jeboori, K.A. Al-Janabi, Chemotherapy 23 (1977) 267–275.
[5] E.J. Corey, D.Y. Gin, R.S. Kania, J. Am. Chem. Soc. 118 (1996) 9202–9203.
[6] (a) A. Pictet, T. Spengler, Ber. Dtsch. Chem. Ges. 44 (1911) 2030–2036;
(b) S.W. Youn, J. Org. Chem. 71 (2006) 2521–2523.
[7] R. Quevedo, E. Baquero, M. Rodriguez, Tetrahedron Lett. 51 (2010) 1774–1778.
[8] X.C. Liu, K. Sun, X.L. Chen, et al., Adv. Synth. Catal. 361 (2019) 3712–3717.
[9] K. Sun, Y.F. Si, X.L. Chen, et al., Adv. Synth. Catal. 361 (2019) 4483–4488.
[10] (a) A.J. Birch, A.H. Jackson, P.V.R. Shannon, J. Chem. Soc. Perkin Trans. 1 (1974) 2185–2190;
(b) D.L. Boger, C.E. Brotherton, M.D. Kelley, Tetrahedron 37 (1981) 3977–3980.
[11] M.J.E. Hewlins, R. Salter, Synth. Stuttg. (2007) 2157–2163.
[12] S. Bhattacharyya, J. Org. Chem. 63 (1998) 7101–7102.