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Concise synthesis of α -cyano tetrahydroisoquinolines with a quaternary center via Strecker reaction†

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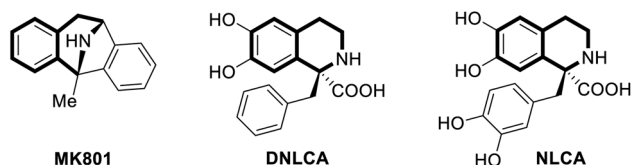
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A concise synthesis of α -cyano tetrahydroisoquinolines with a quaternary center via the Strecker reaction was successfully realized by employing TMSCN as cyano source and KF as fluoride source, furnishing the products with up to 99% yield. An isomerization of α -cyano tetrahydroisoquinoline was observed under alkaline conditions to give the isomer via [1,3]-H shift.

Tetrahydroisoquinoline is an important molecular skeleton widely distributed in natural alkaloids.¹ The abundant biological activity of tetrahydroisoquinoline alkaloids, such as anti-tumor, anti-inflammatory, anti-convulsant and anti-epileptic activity, promotes its potential application in pharmaceutical chemistry and clinical medicine.² Besides, tetrahydroisoquinolines with a quaternary center at the C-1 position also have diverse biological activities (Scheme 1). For example, **MK801**, also known as dizocilpine, was an effective and highly selective NMDA receptor (*N*-methyl-D-aspartic acid receptor).³ As a kind of central nervous system drug, **MK801** has anaesthetic, anti-convulsant and antiepileptic effects. In addition, quaternary substituted tetrahydroisoquinoline carboxylic acids **DNLCA** and **NLCA** are potent noncompetitive dopamine hydroxylase inhibitors, which play an important role in the control of adrenaline synthesis.⁴ Therefore, the development of synthetic methodology for α -substituted tetrahydroisoquinolines with a quaternary center is important and desirable in organic synthesis.

Although the synthesis of tetrahydroisoquinolines have been widely developed,⁵ the research on quaternary substituted

tetrahydroisoquinolines synthesis was rarely explored in the past decades. It still remains a great challenge for the construction of quaternary carbon center attributed to steric hindrance and poor reactivity of substrates.⁶ Only a few researches focused on the study of tetrahydroisoquinolines with quaternary center. Currently, the most frequently used two strategies for the diverse synthesis were as follows: (1) the Lewis acid or enzyme catalysed classical Pictet–Spengler cyclization which provides a concise and straightforward methodology towards tetrahydroisoquinolines;⁷ (2) nucleophilic addition and electrophilic addition/substitution reaction of isoquinoline type substrates. The direct addition of nucleophiles to isoquinolines/isoquinoline type imines was restricted due to the poor reactivity of substrates. With acylating reagents as activator, the reactivity would be effectively enhanced.^{5e,h,8} With regard to isoquinoline type amines which was activated by



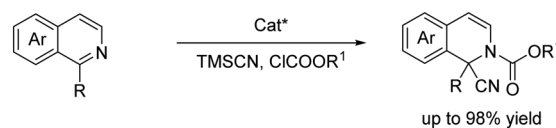
Scheme 1 Representative biologically active molecules of tetrahydroisoquinolines with a quaternary center.

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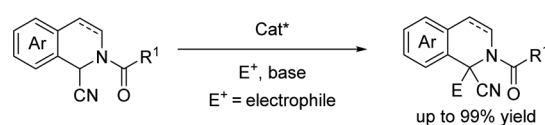
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Previous work

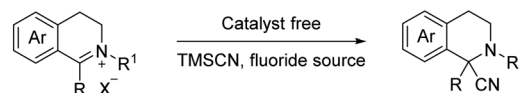
1) Nucleophilic addition via Strecker reaction



2) Electrophilic substitution/addition



This work



Scheme 2 Selected strategies for α -cyano tetrahydroisoquinolines with a quaternary center.



Table 1 Optimization of reaction parameters^a

Entry	Solvent	Base (mol%)	T (°C)	Yield ^b (%)
1	CH ₂ Cl ₂	Na ₂ CO ₃ (50 mol%)	60	80
2	Toluene	Na ₂ CO ₃ (50 mol%)	60	54
3	1,4-Dioxane	Na ₂ CO ₃ (50 mol%)	60	81
4	MeOH	Na ₂ CO ₃ (50 mol%)	60	Mixture
5	ClCH ₂ CH ₂ Cl	Na ₂ CO ₃ (50 mol%)	60	86
6	ClCH ₂ CH ₂ Cl	K ₂ CO ₃ (50 mol%)	60	72
7	ClCH ₂ CH ₂ Cl	Li ₂ CO ₃ (50 mol%)	60	79
8	ClCH ₂ CH ₂ Cl	K ₃ PO ₄ (34 mol%)	60	67
9	ClCH ₂ CH ₂ Cl	Et ₃ N (100 mol%)	60	83
10	ClCH ₂ CH ₂ Cl	Na ₂ CO ₃ (50 mol%)	30	83
11 ^c	ClCH ₂ CH ₂ Cl	Na ₂ CO ₃ (50 mol%)	30	92

^a Reaction conditions: **1a** (0.5 mmol), TMSCN (1.0 mol), 3 mL of solvents, 24 h. ^b Isolated yield. ^c KF (1.0 mol) was added as additive.

acylating reagents to enhance the acidity of C-1 position proton of substrate, base is also essential for the electrophilic addition/substitution to the synthesis of quaternary substituted tetrahydroisoquinolines.⁹ Furthermore, Streuff group reported a concise and direct synthesis *via* titanium(III)-catalyzed reductive umpolung reaction of isoquinoline type imines with nitriles act as effective acylation agents without substrate activation.¹⁰

The Strecker reaction was an efficient and convenient strategy for the synthesis of quaternary amino nitrile adduct with a tetrahydroisoquinoline core *via* the cyanation of prochiral imine or iminium, which could be easily transformed into the corresponding carboxylic acid (Scheme 2).¹¹ In 2001, Shibasaki and co-workers initially reported the bifunctional Al catalysed nucleophilic addition of isoquinolines using an acylating reagent as substrate activator *via* Strecker reaction.⁸ And then Maruoka group^{9b} & Zhang group^{9c} employed α -cyano tetrahydroisoquinolines possessing an *N*-acyl group as substrate in the base conditions, giving the products *via* electrophilic substitution/addition, respectively. And very recently, the Sbei group reported an electro-synthesis of 1,2,3,4-tetrahydroisoquinoline-1-carbonitriles *via* the electro-generated cyanide anions from acetonitrile.¹² Herein, we present a concise synthesis of α -cyano tetrahydroisoquinolines with a quaternary center *via* Strecker reaction, providing the quaternary α -aminonitriles with up to 99% yield.

At the outset of our study, 2-methyl-1-phenyl-3,4-dihydroisoquinolin-2-ium iodide **1a**, was selected as the model substrate for investigation (Table 1, entry 1). To our delight, with TMSCN as the cyano source, the desired product 2-methyl-1-phenyl-tetrahydroisoquinoline-1-carbonitrile **2a** was obtained in the presence of 50 mol% Na₂CO₃ in dichloromethane with 80% yield. With the promising result, further experiments focused on solvents were conducted and 1,2-dichloroethane was proved to be the best choice in 86% isolated yield (entries 2–

5). A survey of base revealed that both inorganic base (entries 5–8) and organic base Et₃N (entry 9) was performed well in the reaction with moderate to good yield. With the temperature decreased to 30 °C, only a slight decrease in activity was observed (entry 10). The nucleophilic ability of TMSCN was much weaker compared with NaCN as the cyano source. And the addition of fluoride source could increase the nucleophilic ability of TMSCN to a great extent due to the strong chemical bond interaction between silicon and fluorine atom, which could promote the generation of cyano. To our delight, the addition of KF to the reaction system improved the reactivity efficiently and a 92% isolated yield of product was obtained (entry 11). Thus, we established the optimal condition for the synthesis of 2-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile **2a**: using 2 equiv. of TMSCN as the cyano source, 0.5 equiv. of Na₂CO₃ as base, 2 equiv. of KF as additive, ClCH₂CH₂Cl as solvent to perform reaction at 30 °C.

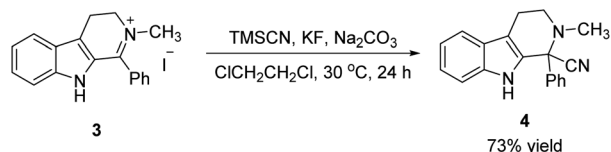
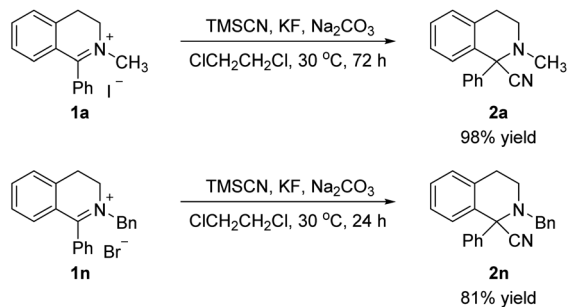
With the optimized condition established, we then set out to demonstrate the generality and practicality of this Strecker reaction of iminiums with a tetrahydroisoquinoline core. A variety of 1-substituted 2-alkyl 3,4-dihydroisoquinolin-2-ium salts were examined under the standard condition, and the results were summarized in Table 2. Generally, the reactions could perform smoothly and effectively, giving the corresponding products in good to excellent yields. The results revealed that the position of the substituents on the aryl ring at C-1 position of tetrahydroisoquinoline core significantly affected the reactivity. For 1-aryl substituted substrate, the increase of sterically hindered effect of substituent resulted in relatively lower yield (entry 2). And it was also noted that the best result of 99% yield was obtained with substrate bearing

Table 2 Synthesis of α -cyano tetrahydroisoquinolines with a quaternary center *via* Strecker reaction^a

Entry	R ¹ /R ²	R ³ /X	R	Yield ^b (%)
1	H/H	CH ₃ /I	C ₆ H ₅	93 (2a)
2	H/H	CH ₃ /I	2-CH ₃ C ₆ H ₄	85 (2b)
3	H/H	CH ₃ /I	3-CH ₃ C ₆ H ₄	99 (2c)
4	H/H	CH ₃ /I	4-CH ₃ C ₆ H ₄	94 (2d)
5	H/H	CH ₃ /I	4-FC ₆ H ₄	88 (2e)
6	H/H	CH ₃ /I	4-ClC ₆ H ₄	94 (2f)
7	H/H	CH ₃ /I	4-CH ₃ OC ₆ H ₄	92 (2g)
8	H/CH ₃	CH ₃ /I	C ₆ H ₅	95 (2h)
9	CH ₃ /CH ₃	CH ₃ /I	C ₆ H ₅	93 (2i)
10	H/CH ₃ O	CH ₃ /I	C ₆ H ₅	86 (2j)
11	H/H	CH ₃ /I	CH ₃	87 (2k)
12	H/H	Et/I	C ₆ H ₅	85 (2l)
13	H/H	CH ₃ (CH ₂) ₉ /I	C ₆ H ₅	80 (2m)
14	H/H	Bn/Br	C ₆ H ₅	85 (2n)

^a Reaction conditions: **1** (0.5 mmol), TMSCN (1.0 mol), KF (1.0 mol), Na₂CO₃ (0.25 mmol), 3 mL of ClCH₂CH₂Cl, 48 h. ^b Isolated yield.



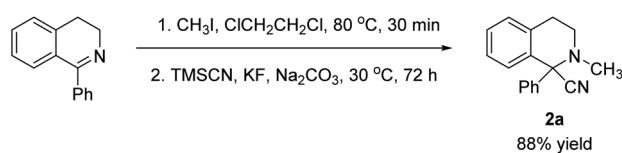
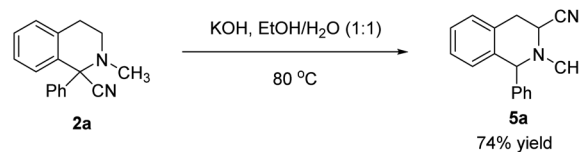
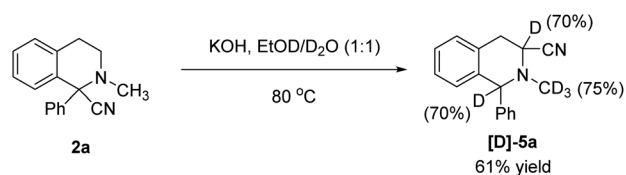
Scheme 3 Synthesis of α -cyano tetrahydro- β -carboline.

Scheme 4 Gram scales.

a methyl group at the *meta*-position of 1-aryl (entry 3). The electronic properties of aryl group at C-1 position also affected the reactivity with marginal effect (entries 4–7). However, the electronic properties of the substituent at C-7 position had great effect on the reactivity and the strongly electron-donating group gave a slightly lower yield (entries 10 vs. 8 and 9). For 1-methyl substituted substrate, the reaction performed well in 87% yield (entry 11). Iminiums bearing a long linear alkyl chain could be proceeded without impediments (entries 12 and 13). With the increasing of the carbon number of alkyl chains of substrate, the reactivity decreased gradually in the meanwhile. Moreover, the benzyl bromide substrate was also investigated and proceeded smoothly in the standard system, giving the desired product in 85% yield (entry 14).

In order to further estimate the application possibility, iminium salt with a β -carboline core (3) was subjected to the standard condition (Scheme 3). To our satisfaction, the desired product (4) was obtained in 73% yield. It also provided a concise and efficient methodology for the synthesis of α -cyano tetrahydro- β -carboline with a quaternary center.

To demonstrate the practical utility, the gram scale reactions were conducted under the optimal condition, providing the corresponding products 2-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (2a, 98% yield) and 2-benzyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (2n, 81% yield), respectively (Scheme 4).

Scheme 5 Cascade reaction for the synthesis of α -cyano tetrahydroisoquinoline.Scheme 6 Isomerization of α -cyano tetrahydroisoquinolines under alkaline condition.

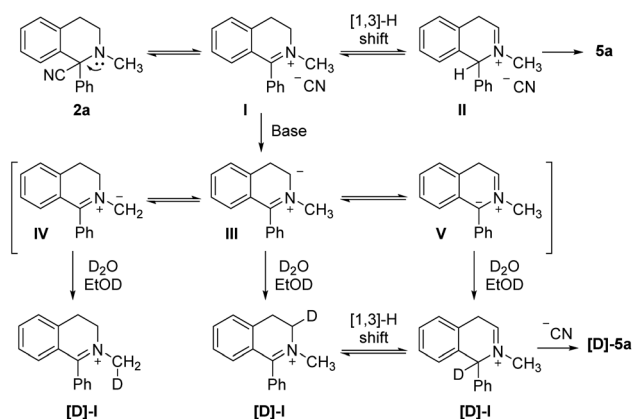
Scheme 7 Mechanistic investigation.

With 1-phenyl-3,4-dihydroisoquinoline as substrate, the cascade reaction for the synthesis of 2-methyl-1-phenyl-tetrahydroisoquinoline-1-carbonitrile (2a) *via* an iminium intermediate generated *in situ* was subsequently investigated (Scheme 5). The reaction was performed well, giving the product in 88% yield.

To further highlight the practical utility of the addition product α -cyano tetrahydroisoquinolines, the hydrolysis of 2-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (2a) was conducted under alkaline conditions in the presence of potassium hydroxide (Scheme 6). To our surprise, the reaction performed smoothly to provide the isomerization product 2-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carbonitrile (5a) in good yield instead of hydrolysis product.¹³

Then, to gain insight to the isomerization reaction mechanism, an isotopic labelling experiment was conducted with EtOD/D₂O as solvent (Scheme 7). The product was obtained in 61% yield and with 70% deuterium incorporation in C-1 and C-3 positions and 75% deuterium incorporation on the methyl group.

Based on the experimental results and structure of the product, the mechanism was proposed that the reaction



Scheme 8 Proposed reaction pathways.



experienced the process of base promoted tautomerization of iminium isomers and the [1,3]-H shift *via* a six-membered cyclic transition state under alkaline condition as depicted in Scheme 8. Considering the steric hindrance effect and stability of the iminium intermediate, the reaction was then followed by a nucleophilic addition of CN at C-3 position toward the isomerized product.

Conclusions

In summary, by employing TMSCN as the cyano source, we have successfully developed an efficient and convenient method for synthesis of α -cyano tetrahydroisoquinolines with a quaternary center *via* Strecker reaction in good to excellent yields. Meanwhile, a compatible one-pot, single-operation cascade reaction for the synthesis of quaternary α -cyano tetrahydroisoquinolines was realized, furnishing the desired product in 88% yield. Interestingly, an isomerization of α -cyano tetrahydroisoquinoline was observed under alkaline condition *via* [1,3]-H shift. Further studies to expand the scope to other amines with a quaternary center are ongoing in our laboratory.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

- (a) J. D. Scott and R. M. Williams, *Chem. Rev.*, 2002, **102**, 1669; (b) T. Kametani, H. Sugi and S. Shibuya, *Tetrahedron*, 1971, **27**, 2409; (c) S. Peng, M. Guo and E. Winterfeldt, *Liebigs Ann. Chem.*, 1993, 137.
- (a) V. G. Kartsev, *Med. Chem. Res.*, 2004, **13**, 325; (b) M. Ohkubo, A. Kuno, K. Katsuta, Y. Ueda, K. Shirakawa, H. Nakanishi, I. Nakanishi, T. Kinoshita and H. Takasugi, *Chem. Pharm. Bull.*, 1996, **44**, 95.
- Selected reports: (a) W. J. Thompson, P. S. Anderson, S. F. Britcher, T. A. Lyle, J. E. Thies, C. A. Magill, S. L. Varga, J. E. Schwering, P. A. Lyle, M. E. Christy, B. E. Evans, C. D. Colton, M. K. Holloway, J. P. Springer, J. M. Hirshfield, R. G. Ball, J. S. Amato, R. D. Larsen, E. H. F. Wong, J. A. Kemp, M. D. Tricklebank, L. Singh, R. Oles, T. Priestly, G. R. Marshall, A. R. Knight, D. N. Middlemiss, G. N. Woodruff and L. L. Iversen, *J. Med. Chem.*, 1990, **33**, 789; (b) J. A. Monn, A. Thurkauf, M. V. Mattson, A. E. Jacobson and K. C. Rice, *J. Med. Chem.*, 1990, **33**, 1069; (c) J. P. Rung, A. Carlsson, K. R. Markinhulta and M. L. Carlsson, *Prog. Neuro-Psychopharmacol. Biol. Psychiatry*, 2005, **29**, 827.
- (a) J. C. Crscia, W. Burke, G. Jamroz, J. M. Lasala, J. Mcfarlane, J. Mitchell, M. M. O'Toole and M. L. Wilson, *Nature*, 1977, **269**, 617; (b) J. M. Lasala and J. C. Crscia, *Science*, 1979, **203**, 283.
- For reviews, see: (a) M. Chrzanowska and M. D. Rozwadowska, *Chem. Rev.*, 2004, **104**, 3341; (b) Y.-G. Zhou, *Acc. Chem. Res.*, 2007, **40**, 1357; (c) W. Liu, S. Liu, R. Jin, H. Guo and J. Zhao, *Org. Chem. Front.*, 2015, **2**, 288; (d) D. Li, X. Chen and W. Gao, *Synthesis*, 2020, **52**, 3337. Selected reports on synthesis of tetrahydroisoquinolines: ; (e) S.-M. Lu, Y.-Q. Wang, X.-W. Han and Y.-G. Zhou, *Angew. Chem., Int. Ed.*, 2006, **45**, 2260; (f) P.-C. Yan, J.-H. Xie, G.-H. Hou, L.-X. Wang and Q.-L. Zhou, *Adv. Synth. Catal.*, 2009, **351**, 3243; (g) M. Chang, W. Li and X. Zhang, *Angew. Chem., Int. Ed.*, 2011, **50**, 10679; (h) Z.-S. Ye, R.-N. Guo, X.-F. Cai, M.-W. Chen, L. Shi and Y.-G. Zhou, *Angew. Chem., Int. Ed.*, 2013, **52**, 3685; (i) Q.-H. Zheng, W. Meng, G.-J. Jiang and Z.-X. Yu, *Org. Lett.*, 2013, **15**, 5928; (j) Z.-Y. Ding, T. Wang, Y.-M. He, F. Chen, H.-F. Zhou, Q.-H. Fan, Q. Guo and A. S. C. Chan, *Adv. Synth. Catal.*, 2013, **355**, 3727; (k) A. Iimuro, K. Yamaji, S. Kandula, T. Nagano, Y. Kita and K. Mashima, *Angew. Chem., Int. Ed.*, 2013, **52**, 2046; (l) W. Lin, T. Cao, W. Fan, Y. Han, J. Kuang, H. Luo, B. Miao, X. Tang, Q. Yu, W. Yuan, J. Zhang, C. Zhu and S. Ma, *Angew. Chem., Int. Ed.*, 2014, **53**, 277; (m) Y. Ji, L. Shi, M.-W. Chen, G.-S. Feng and Y.-G. Zhou, *J. Am. Chem. Soc.*, 2015, **137**, 10496; (n) M.-W. Chen, Y. Ji, J. Wang, Q.-A. Chen, L. Shi and Y.-G. Zhou, *Org. Lett.*, 2017, **19**, 4988; (o) A. N. Kim, A. Ngamthiporn, E. R. Welin, M. T. Daiger, C. U. Grünanger, M. D. Bartberger, S. C. Virgil and B. M. Stoltz, *ACS Catal.*, 2020, **10**, 3241.
- Review for the construction of quaternary centers: (a) K. Fuji, *Chem. Rev.*, 1993, **93**, 2037. Selected examples: ; (b) H. R. Tan, H. F. Ng, J. Chang and J. Wang, *Chem.-Eur. J.*, 2012, **18**, 3865; (c) Z. Yan, B. Wu, X. Gao and Y.-G. Zhou, *Chem. Commun.*, 2016, **52**, 10882; (d) Z. Yan, X. Gao and Y. -G. Zhou, *Chin. J. Catal.*, 2017, **38**, 784; (e) X.-W. Wang, M.-W. Chen, B. Wu, B. Wang and Y.-G. Zhou, *J. Org. Chem.*, 2019, **84**, 8300; (f) X.-W. Wang, M.-W. Chen, B. Wu, B. Wang, B. Wan and Y.-G. Zhou, *Tetrahedron Lett.*, 2021, **62**, 152793; (g) X.-W. Wang, X. Li, M.-W. Chen, B. Wu and Y.-G. Zhou, *J. Org. Chem.*, 2021, **86**, 6897.
- Selected reports on Pictet-Spengler cyclization: (a) Y. Horiguchi, H. Kodama, M. Nakamura, T. Yoshimura, K. Hanezi, H. Hamada, T. Saitoh and T. Sano, *Chem. Pharm. Bull.*, 2002, **50**, 253; (b) A. Hegedus and Z. Hell, *Tetrahedron Lett.*, 2004, **45**, 8553; (c) M. J. V. Eynden, K. Kunchithapatham and J. P. Stambuli, *J. Org. Chem.*, 2010, **75**, 8542; (d) B. R. Lichman, J. Zhao, H. C. Hailes and J. M. Ward, *Nat. Commun.*, 2017, **8**, 14883.



- 8 K. Funabashi, H. Ratni, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc.*, 2001, **123**, 10784.
- 9 (a) A. I. Meyers, M. A. Gonzalez, V. Struzka, A. Akahane, J. Guiles and J. S. Warmus, *Tetrahedron Lett.*, 1991, **32**, 5501; (b) S. Shirakawa, K. Liu, H. Ito, T. N. Le and K. Maruoka, *Adv. Synth. Catal.*, 2011, **353**, 2614; (c) T.-Y. Qin, W.-W. Liao, Y.-J. Zhang and S. X.-A. Zhang, *Org. Biomol. Chem.*, 2013, **11**, 984; (d) X. Li and I. Coldham, *J. Am. Chem. Soc.*, 2014, **136**, 5551.
- 10 H.-T. Luu, S. Wiesler, G. Frey and J. Streuff, *Org. Lett.*, 2015, **17**, 2478.
- 11 Select reviews for Strecker reactions: (a) H. Gröger, *Chem. Rev.*, 2003, **103**, 2795; (b) J. Wang, X. Liu and X. Feng, *Chem. Rev.*, 2011, **111**, 6947; (c) N. Kurono and T. Ohkuma, *ACS Catal.*, 2016, **6**, 989. Select examples: ; (d) H.-W. Bersch, R. RiRmann and D. Schon, *Arch. Pharm.*, 1982, **315**, 749; (e) H. Moehrle and H. Breves, *Pharmazie*, 2005, **60**, 23; (f) N. G. Voznesenskaya, O. I. Shmatova, A. A. Sosnova and V. G. Nenajdenko, *Eur. J. Org. Chem.*, 2019, 625.
- 12 N. Sbei, A. A. Titov, E. B. Markova, M. N. Elinson and L. G. Voskressensky, *ChemistrySelect*, 2020, **5**, 4493.
- 13 Selected researches for rearrangement of isoquinoline-tape substrates:(a) M. Sainseury, D. W. Brown, S. F. Dyke, R. G. Kinsman and B. J. Moon, *Tetrahedron*, 1968, **24**, 6695; (b) J. Knabe and R. Dörr, *Arch. Pharm.*, 1973, **306**, 784; (c) E. Langhals, H. Langhals and C. Riichardt, *Chem. Ber.*, 1984, **117**, 1436; (d) N. Blank, B. F. Straub and T. Opatz, *Eur. J. Org. Chem.*, 2011, 7355; (e) J. C. O. Pacheco, G. Lahm and T. Opatz, *J. Org. Chem.*, 2013, **78**, 4985.

