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PII: S0040-4039(14)00195-6
DOI: http://dx.doi.org/10.1016/j.tetlet.2014.01.139
Reference: TETL 44172

To appear in: *Tetrahedron Letters*

Received Date: 28 October 2013
Revised Date: 16 January 2014
Accepted Date: 29 January 2014

Please cite this article as: Maleki, A., Rezayan, A.H., Synthesis of pyrido[2',1':2,3]imidazo[4,5-*c*]isoquinolines via a one-pot, three-component reaction, *Tetrahedron Letters* (2014), doi: http://dx.doi.org/10.1016/j.tetlet.2014.01.139

Graphical Abstract

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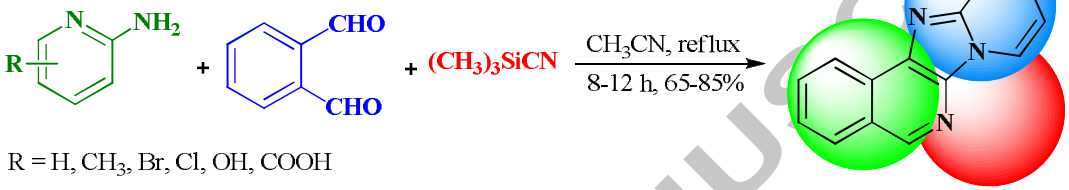

R = H, CH_3, Br, Cl, OH, COOH

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Synthesis of pyrido[2',1':2,3]imidazo[4,5-*c*]isoquinolines via a one-pot, three-component reaction

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ARTICLE INFO

Article history:
Received
Revised
Accepted
Available online

Keywords:
Pyrido[2',1':2,3]imidazo[4,5-*c*]isoquinoline
Multicomponent reaction
Trimethylsilyl cyanide
Aminopyridine
Phthalaldehyde

ABSTRACT

A one-pot, three-component reaction for the synthesis of pyrido[2',1':2,3]imidazo[4,5-*c*]isoquinolines starting from 2-aminopyridines, phthalaldehyde and trimethylsilyl cyanide in good to high yields is described.

Nitrogen-containing fused heterocyclic compounds play important roles in drug discovery processes.[1,2] For example, benzimidazo[2,1-*a*]isoquinolines[3] and pyrido[1,2-*e*]purines[4] have potential anticancer activities, 6*H*-pyrido[2',1':2,3]imidazo[4,5-*c*]-isoquinoline-5(6*H*)-ones are antitumor agents that have been prepared by the reaction of 2-formylbenzoic acid, 2-aminopyridines and potassium cyanide[5a] or trimethylsilyl cyanide (TMSCN)/KF.[5b] In addition, the same compounds have been prepared starting from 2-aminoazines, 2-formyl benzoic acid or its esters and isocyanides.[6] Furthermore, the synthesis of aminoimidazo[5,1-*a*]isoquinolinium salts, as blood sugar lowering agents in the treatment of diabetes,[7] using isoquinoline and isocyanides in the presence of sulfonic acids, has been reported by Shaabani et al.[8]

Due to their remarkable central nervous system activity, imidazopyridines have been the subject of intensive investigation in synthetic and medicinal chemistry.[9-16] They are now one of the most widely prescribed classes of psychotropics and also act as potent anti-inflammatory[9] and antibacterial agents,[10] inhibitors of gastric acid secretions,[11] selective cyclin-dependent kinase inhibitors,[12] calcium channel blockers,[13] β-amyloid formation inhibitors,[14] bradykinin B2 receptor antagonists[15] and as biologically and pharmaceutically active agents.[16]

In continuation of our studies to develop new procedures for multicomponent reactions (MCRs),[17] herein, we report the facile synthesis of pyrido[2',1':2,3]imidazo[4,5-*c*]isoquinolines **4a-i** via the one-pot, three-component reaction of 2-aminopyridines **1**, phthalaldehyde (**2**) and TMSCN (**3**) in refluxing CH_3CN (Scheme 1).

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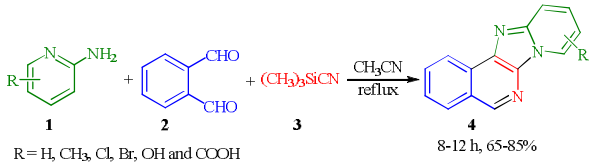
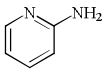
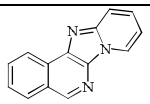
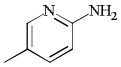
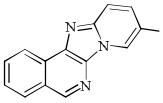
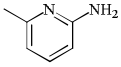
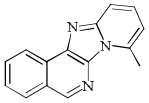
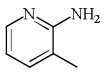
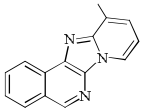
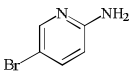
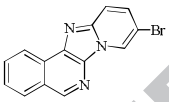
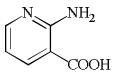
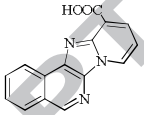
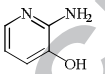
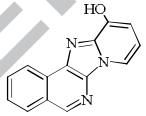
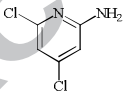
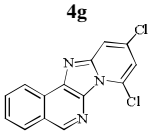
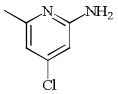
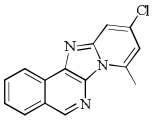


Scheme 1. Synthesis of pyrido[2',1':2,3]imidazo[4,5-*c*]isoquinolines **4a-i**.

Table 1

Synthesis of pyrido[2',1':2,3]imidazo[4,5-*c*]isoquinolines **4a-i**

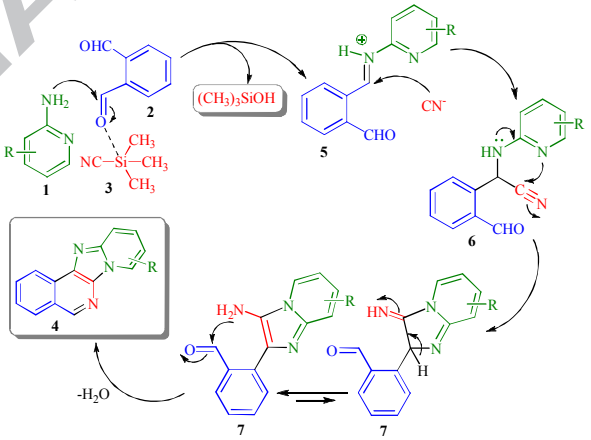
Entry	2-Aminopyridine	Product	Time (h)	Yield[a] (%)
1		 **4a**	8	75
2		 **4b**	10	80
3		 **4c**	12	67
4		 **4d**	10	73
5		 **4e**	9	79
6		 **4f**	8	85
7		 **4g**	12	72
8		 **4h**	11	68
9		 **4i**	12	65

[a] Isolated yield.

In a pilot experiment, the reaction of 2-aminopyridine (**1**, R = H) and phthalaldehyde (**2**) with TMSCN in refluxing CH_3CN afforded pyrido[2',1':2,3]imidazo[4,5-*c*]isoquinoline (**4a**) in 75% yield after eight hours. In the same manner, a variety of 2-aminopyridines were reacted with phthalaldehyde and TMSCN in a one-pot operation to give the corresponding pyrido[2',1':2,3]imidazo[4,5-*c*]isoquinolines **4b-i** in good to excellent yields.

As shown in Table 1, 2-aminopyridines possessing various substituents were readily used in this reaction to give the desired products. Due to steric hindrance or a combination of steric hindrance and electronic effects, 2-amino-6-methylpyridine, 2-amino-4,6-dichloropyridine and 2-amino-4-chloro-6-methylpyridine gave the desired products in lower yields (entries 3, 8 and 9). However, in the case of 2-aminopyridine-3-carboxylic acid, the acidity of the carboxylic group enhanced the imine formation and gave the corresponding compound **4f** in a high 85% yield (entry 6).

A possible mechanism for the formation of pyrido[2',1':2,3]imidazo[4,5-*c*]isoquinolines **4a-i** using 2-aminopyridines **1**, phthalaldehyde (**2**) and TMSCN (**3**) is shown in Scheme 2. It is conceivable that the initial event is the formation of iminium ion **5** from 2-aminopyridine **1** and phthalaldehyde (**2**). On the basis of the well established chemistry of the reactions of TMSCN (**3**) with imines,[17d,e,18] intermediate **6** was obtained by nucleophilic attack of cyanide on **5**. The pyridine nitrogen of **6** is in a favorable position for cyclization to produce intermediate **7**. Subsequent, intramolecular nucleophilic addition of the NH_2 of the enamine tautomer of **7** to the second carbonyl of phthalaldehyde gives product **4**.[19,20]



Scheme 2. A plausible mechanism for the formation of products **4a-i**.

In conclusion, a new class of pyrido[2',1':2,3]imidazo[4,5-*c*]isoquinolines was synthesized starting from 2-aminopyridines, phthalaldehyde and TMSCN. The results in Table 1 show the scope and generality of the reaction with respect to various 2-aminopyridines. This one-pot, three-component protocol includes advantages such as simple and readily available precursors, an easy work-up procedure, good to high yields and mild reaction conditions. Another advantage of this reaction was its high selectivity, and no undesired side products were observed.

Acknowledgements

The authors gratefully acknowledge the financial support from the Iran National Science Foundation (INSF) and partial support

from the Research Council of the Iran University of Science and Technology.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at www.elsevier.com/locate/tetlet. These include spectral data of the products **4a-i**, MOL files and InChiKeys of several compounds described in this article.

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19. *General procedure for the synthesis of compounds* **4a-i**: A mixture of a 2-aminopyridine (1 mmol), phthalaldehyde (**2**) (1 mmol), and TMSCN (**3**) (1 mmol) in CH_3CN (10 mL) was refluxed for the appropriate amount of time. After completion of the reaction, as indicated by TLC (EtOAc/*n*-hexane, 4/1), the mixture was filtered and the residue purified by washing with *n*-hexane (5 mL), and then crystallized from EtOH or CH_3CN to give pure crystalline products **4a-i**.
20. *Spectral data of Pyrido[2',1':2,3]imidazo[4,5-c]isoquinoline (**4a**).* Light yellow crystals; mp = 255-256 °C; IR (KBr): ν_{max} (cm^{-1}) = 3082, 2972, 2873, 1665, 1620, 1562, 1384, 1334, 1262; ^1H NMR (300 MHz, DMSO-d_6): δ_H (ppm) = 8.96 (1H, s, H-C=N), 8.30-6.60 (8H, m, H-Ar); MS (EI, 70 eV): *m/z* (%) = 219 (M^+, 67), 144 (54), 127 (100), 105 (32), 91 (67), 76 (58), 41 (50). Anal. Calcd for $C_{14}H_9N_3$: C, 76.70; H, 4.14; N, 19.17. Found C, 76.62; H, 4.22; N, 19.43.

Highlights

- Pyridoimidazoisoquinolines were synthesized in high yields and mild conditions.
- The scope and generality of the reaction is investigated.
- Precursors were simple and readily available.
- The reaction was highly selective; and workup procedure was easy.
- No undesired side products were observed.