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Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: https://www.tandfonline.com/loi/lsyc20

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To cite this article: Shravani Madhunala, Siva Hariprasad Kurma, Varsha Reddy Etikala & China Raju Bhimapaka (2019): Condensation of 4-chloro-2*H*-chromene-3-carbaldehydes and ethyl-3-aminocrotonates with *p*-TsOH: a facile approach for the synthesis of chromenyldihydropyridines, Synthetic Communications, DOI: 10.1080/00397911.2019.1631850

To link to this article: https://doi.org/10.1080/00397911.2019.1631850

Published online: 09 Jul 2019.

SYNTHETIC COMMUNICATIONS®
https://doi.org/10.1080/00397911.2019.1631850

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Condensation of 4-chloro-2*H*-chromene-3-carbaldehydes and ethyl-3-aminocrotonates with *p*-TsOH: a facile approach for the synthesis of chromenyldihydropyridines

Shravani Madhunala, Siva Hariprasad Kurma, Varsha Reddy Etikala, and China Raju Bhimapaka

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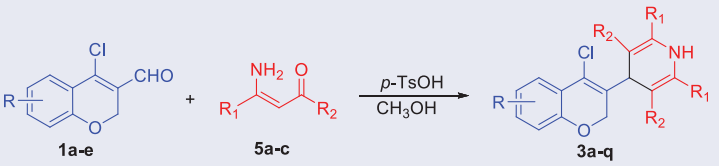
ABSTRACT

The investigated reaction of 4-chloro-2*H*-chromene-3-carbaldehyde **1a** with ethyl 3-oxobutanoate **2a** in the presence of ammonium acetate provided two compounds, 2*H*-chromenyldihydropyridine dicarboxylate **3a** and chromenopyridine carboxylate **4a**. However, the reaction of **1a** with ethyl-3-aminocrotonate **5a** in the presence of *p*-TsOH provided selectively 2*H*-chromenyldihydropyridine dicarboxylate **3a** with very good yield. The established method was applied for the preparation of series of 2*H*-chromenyldihydropyridine dicarboxylates **3a**–**q**.

GRAPHICAL ABSTRACT



ARTICLE HISTORY
Received 28 March 2019

KEYWORDS
4-Chloro-2H-chromene-3-carbaldehydes; ethyl-3-aminocrotonates; 2*H*-chromenyldihydropyridine dicarboxylates; p-TsOH

Introduction

Dihydropyridines[1–4] are biologically important heterocyclic compounds and structural motif present in various natural products and pharmaceuticals. 4-Chloro-2*H*-chromene-3-carbaldehydes are useful chemical substrates[5] having two reactive sites at C-3 (Conjugated carbonyl group) and C-4 (Chloro functional group) and have been prepared various heterocyclic compounds which are well documented in the literature.[6–10] As part of our ongoing research work on 4-chloro-2*H*-chromene-3-carbaldehydes, author group prepared 2*H*-chromenylacrylates,[11] 2*H*-chromenylmethylene benzohydrizides[12] and 2*H*-chromenyl azlactones,[13] by chemical modification of 2*H*-chromene-3-carbaldehydes. Generally, condensation of carbaldehyde compounds with ethyl-3-aminocrotonate gives dihydropyridines. However, David and his research group reported

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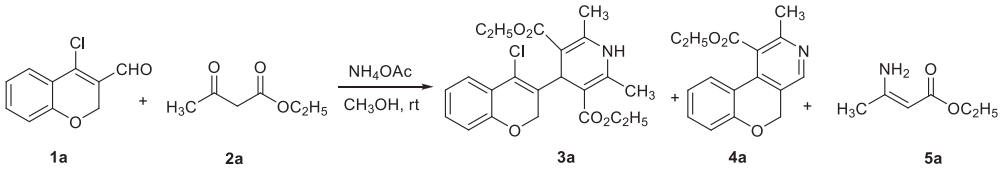


Scheme 1. Reaction of 1a with 2a in presence of ammonium acetate.

5*H*-chromenopyridines[5] by the condensation of 4-chloro-2*H*-chromene-3-carbaldehyde with ethyl-3-aminocrotonate in methanol under reflux conditions. Michael addition of ethyl-3-aminocrotonate to the reactant of 4-chloro-2*H*-chromene-3-carbaldehyde provided the dihydropyridyl moiety with the elimination of HCl. We were delighted this observation and the reaction of 4-chloro-2*H*-chromene-3-carbaldehydes have been reinvestigated with various ethyl-3-aminocrotonates in the presence of various catalysts. Interestingly, these reactions provided 2*H*-chromenyldihydropyridines instead of 5*H*-chromenopyridines. The observations about these reactions and results obtained were presented below.

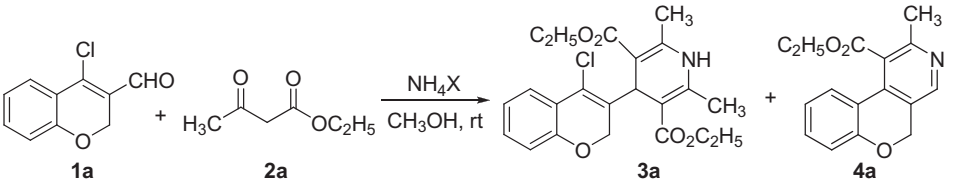
Results and discussions

In an initial experiment, we have conducted three-component, one-pot reaction of 4-chloro-2*H*-chromene-3-carbaldehyde **1a** (1 mmol) with ethyl 3-oxo-butanoate **2a** (2 mmol) in the presence of ammonium acetate (4 mmol) in methanol at room temperature (Scheme 1). This reaction yielded two compounds, 2*H*-chromenyldihydropyridine **3a** (65%) and 5*H*-chromenopyridine **4a** (20%).[5] We also observed the formation of ethyl-3-aminocrotonate **5a** in minor quantity (10%). This probably formed between ethyl 3-oxo-butanoate and ammonium acetate during the reaction. These compounds were isolated and characterized by spectral data.

In order to obtain the compound **3a** selectively, next, the reaction of **1a** with **2a** has been tested with various ammonium salts and the results are tabulated in Table 1. We observed the formation of compound **3a** in major quantity and **4a** in minor quantity with NH_4F (**3a** 62%, **4a** 22% yield) and $(NH_4)_2CO_3$ (**3a** 70%, **4a** 15% yield, Table 1, entry 2, 8). NH_4Cl, NH_4Br, $(NH_4)_2NO_3$ and $(NH_4)_2SO_4$ did not work (Table 1, entry 3–5 and 7) under these conditions. We believe that these ammonium salts are less reactive with **2a** to form **5a** to precede the reaction to give the final compound **3a**. Next, we have tested this reaction with various catalysts in the presence of $(NH_4)_2CO_3$ (Table 1, entry 9–22) in order to get the compound **3a** with selectively. Among such catalysts, AcOH, $CaCl_2$, $SnCl_2$, $CuCl_2$, $ZnCl_2$, $CeCl_3$ and I_2 produced both the compounds (**3a** 40–70%) and (**4a** 26–38% yield, Table 1, entry 10, 12–16, 18). Interestingly, NH_2SO_3H and $H_3PW_{12}O_{40}$ selectively provided only compound **3a** with poor yields and longer reaction time (Table 1, entry 19–20). The remaining catalysts *p*-TSA, TFA, $BiCl_3$, $ZrOCl_2$ and $Bi(OTf)_3$ did not work (Table 1, entry 9, 11, 17, 21–22) under these conditions.

The above reactions produced mixture of compounds **3a** and **4a**. In order to obtained compound **3a,** we have next planned the reaction of **1a** with ethyl-3-aminocrotonate. The required ethyl-3-aminocrotonate **5a** was prepared by the reaction of ethyl

Table 1. Reaction of **1a** and **2a** with various ammonium salts.



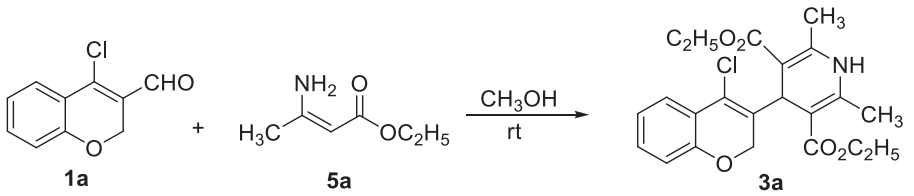
Entry	NH_4X	Catalyst	Time (h)	3a (%)[a]	4a (%)[a]
1	NH_4OH	---	24	66	28
2	NH_4F	---	28	62	22
3	NH_4Cl	---	24	---	---
4	NH_4Br	---	60	---	---
5	NH_4NO_3	---	72	---	---
6	NH_4OAc	---	72	65	28
7	$NH_4(SO_4)_2$	---	51	---	---
8	$(NH_4)_2CO_3$	---	8	70	15
9	$(NH_4)_2CO_3$	*p*-TsOH	24	---	---
10	$(NH_4)_2CO_3$	AcOH	22	40	26
11	$(NH_4)_2CO_3$	TFA	48	---	---
12	$(NH_4)_2CO_3$	$CaCl_2$	48	50	32
13	$(NH_4)_2CO_3$	$SnCl_2$	8	50	30
14	$(NH_4)_2CO_3$	$CuCl_2.H_2O$	8	66	29
15	$(NH_4)_2CO_3$	$ZnCl_2$	8	50	31
16	$(NH_4)_2CO_3$	$CeCl_3$	8	60	38
17	$(NH_4)_2CO_3$	$BiCl_3$	24	---	---
18	$(NH_4)_2CO_3$	I_2	8	70	18
19	$(NH_4)_2CO_3$	NH_2SO_3H	24	30	---
20	$(NH_4)_2CO_3$	$H_3PW_{12}O_{40}$	24	20	---
21	$(NH_4)_2CO_3$	$ZrOCl_2.6H_2O$	24	---	---
22	$(NH_4)_2CO_3$	$Bi(OTf)_3$	24	---	---

[a]Isolated yields.

3-oxobutanoate **2a** with ammonium hydroxide.[5] Initially, the reaction of **1a** (1 mmol) with **5a** (2 mmol) carried out in methanol at room temperature without using any catalyst. Interestingly, this reaction was provided compound **3a** selectively in 48% yield (60 h, Scheme 2).

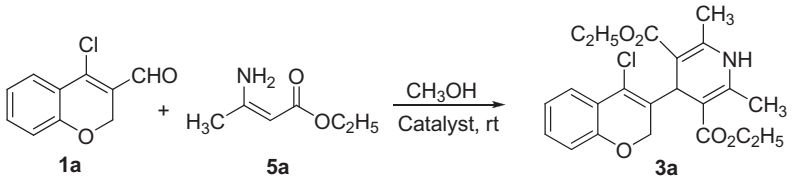
Next, we have carried out the reaction of **1a** (1 mmol) with **5a** (2 mmol) in the presence of various catalysts such as $CaCl_2$, $SnCl_2$, $CuCl_2$, I_2, $ZnCl_2$, $H_3PW_{12}O_{40}$, $BiCl_3$, NH_2SO_3H, $ZrOCl_2$ and $Bi(OTf)_3$ AcOH, $CeCl_3.7H_2O$ (Table 2, entry 2–14) in methanol at room temperature. All these catalysts provided the compound **3a** in moderate to good yields except AcOH and $CeCl_3.7H_2O$. However, we found *p*-TsOH is the best catalyst and provided compound **3a** in very good yield (75%, Table 2, entry 2). The plausible mechanism for the formation of compound **3a** is depicted in Scheme 3.

The result was encouraged us to establish the present protocol with various 4-chloro-2*H*-chromene-3-carboxaldehydes with ethyl-3-aminocrotonates to prepare series of



Scheme 2. Preparation of 3a by the reaction of 1a with ethyl-3-aminocrotonate 5a.

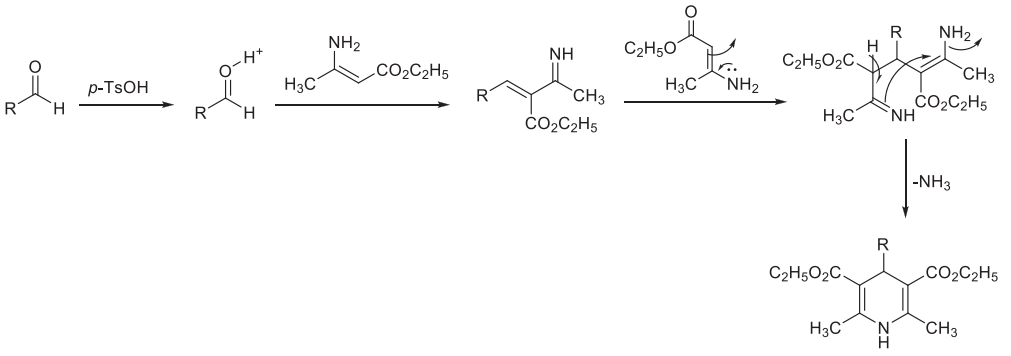
Table 2. Preparation of 2*H*-chromenyldihydropyridine **3a**.



Entry	Catalyst	Time (h)	Yield (%)[a]
1	---	60	48
2	*p*-TsOH	4	75
3	AcOH	6	---
4	$CaCl_2$	24	45
5	$SnCl_2$	24	42
6	$CuCl_2.H_2O$	24	40
7	I_2	24	42
8	$ZnCl_2$	24	46
9	$CeCl_3.7H_2O$	24	---
10	$H_3PW_{12}O_{40}$	24	55
11	$BiCl_3$	24	50
12	NH_2SO_3H	24	60
13	$ZrOCl_2.6H_2O$	24	48
14	$Bi(OTf)_3$	24	57

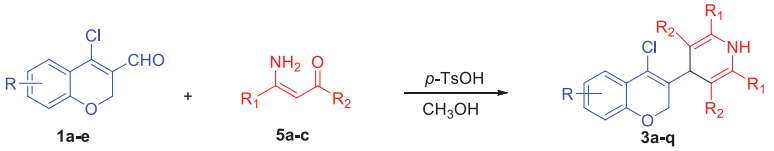
[a]Isolated yields.

2*H*-chromenyldihydropyridines. Accordingly, the starting materials 4-chloro-2*H*-chromene-3-carbaldehydes **1b–e** were prepared from chroman-4-ones under Vilsmeier reaction conditions.[5] Similarly, various aminocrotonates such as methyl 3-aminobut-2-enoate **5b**, ethyl 3-amino-3-phenylacrylate **5c** and ethyl 3-amino-4,4,4-trifluorobut-2-enoate **5d**, ethyl 3-(phenylamino)but-2-enoate **5e,** ethyl 3-(benzylamino)but-2-enoate **5f** and 4-aminopent-3-en-2-one (amino ketone) **5h** were prepared starting from corresponding β-ketoesters and 1,3-diketone as per the literature procedures.[14–24] Thus prepared carbaldehydes **1b–e** were reacted with **5a–h** in the presence of *p*-TsOH under optimized conditions. The carbaldehydes **1b–e** were preceded smoothly with **5a–c** and provided the series of 2*H*-chromenyldihydropyridines **3b–q** in moderate to very good yields (Table 3). The electron donating groups provided good yields when compared to withdrawing groups. However,

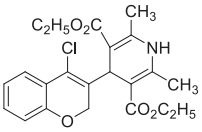
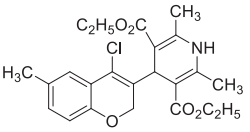
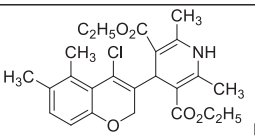
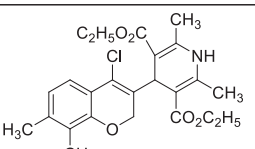
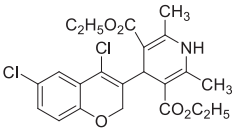
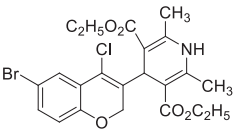
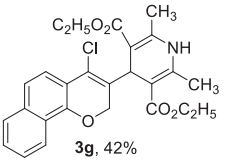
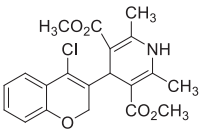
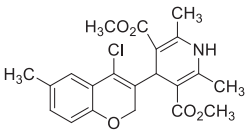
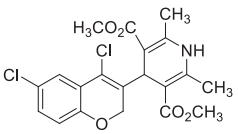
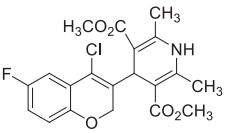
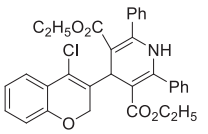
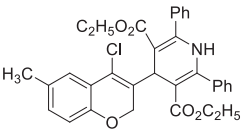
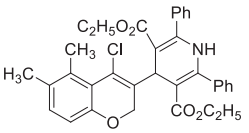
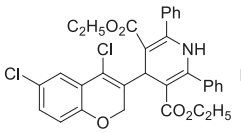
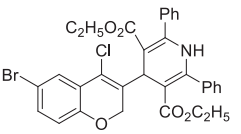
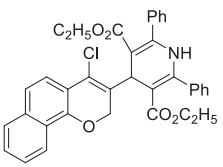


Scheme 3. Plausible mechanism.

Table 3. Preparation of 2*H*-chromenyldihydropyridines **3a–q**.



1a-e + 5a-c → 3a-q

 **3a**, 75%	 **3b**, 78%	 **3c**, 85%	 **3d**, 82%
 **3e**, 35%	 **3f**, 34%	 **3g**, 42%	 **3h**, 68%
 **3i**, 51%	 **3j**, 32%	 **3k**, 53%	 **3l**, 58%
 **3m**, 61%	 **3n**, 65%	 **3o**, 57%	 **3p**, 46%
 **3q**, 34%			

aminocrotonates **5d–h** did not provided the corresponding compounds. All the compounds **3a–q** are unknown and well characterized by spectral data (see SI).

Conclusion

In conclusion, we have developed a convenient approach for the preparation of 2*H*-chromenyldihydropyridines by the reaction of 4-chloro-2*H*-chromene-3-carbaldehydes with ethyl-3-aminocrotonates in the presence of *p*-TsOH in methanol at room temperature. The mild reaction conditions and commercially available reagents are the notable points. The prepared compounds are medicinally and pharmaceutically important heterocycles.

Experimental

General procedure for the preparation of diethyl-4-(4-chloro-2H-chromen-3-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (3a)

Ethyl-3-aminocrotonate (**5a**, 2 mmol) was added to a stirred solution of 4-chloro-2*H*-chromene-3-carbaldehyde (**1a**, 1 mmol), *p*-TsOH (1 mmol) in methanol at room temperature. The contents were stirred until completion of the reaction (TLC, 4 h). The solvent was removed under reduced pressure and the reaction mass diluted with ethyl acetate and washed with water. Layers were separated and the organic layer was dried over sodium sulfate. The crude product was purified by column chromatography (60:120 silica gel, 1:9 ethyl acetate: hexane) afforded 2*H*-chromenyldihydropyridine **3a** as colorless solid. The remaining compounds **3b–q** were prepared from corresponding 2*H*-chromene-3-carbaldehydes **1b–e** with ethyl-3-aminocrotonates **5a–c** under optimized reaction conditions.

Spectral data for the synthesized compounds can be accessed on the publisher's website.

Acknowledgment

The authors thank Director, CSIR-IICT for constant encouragement and support.

Funding

B. China Raju acknowledges SERB, New Delhi for financial support [EEQ/2017/000314]. IICT manuscript communication no. IICT/Pubs./2018/265.

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