Pergamon

Tetrahedron Letters 42 (2001) 5187–5189

TETRAHEDRON LETTERS

Efficient synthesis of 3-(4,5-dihydro-1*H*-imidazole-2-yl)-1*H*-indoles

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Received 31 May 2001; accepted 4 June 2001

Abstract—A simple method for the synthesis of various 3-(4,5-dihydro-1*H*-imidazole-2-yl)-1*H*-indoles is described. Treatment of different substituted indoles with 1-acetyl-imidazolidin-2-one in the presence of phosphorus oxychloride afforded after hydrolysis in ethanol the corresponding 3-(4,5-dihydro-1*H*-imidazole-2-yl)-1*H*-indoles in moderate to good yields. © 2001 Published by Elsevier Science Ltd.

1. Introduction

Over recent years a number of imidazoline containing compounds have been identified that stimulate and regulate insulin secretion in a glucose dependent manner.[1] However, despite their promise, no imidazoline compound has yet come into clinical use as an effective agent in treatment of type II diabetes due to several side effects.

Our continuing interest in the search for new insulin secretagogues with the desired profile led us to describe the new imidazoline containing insulin secretagogue 5-chloro-2-methyl-3-(4,5-dihydro-1*H*-imidazole-2-yl)-1*H*-indole **1**.[2] This compound belongs to a series of various *C*-connected 3-(4,5-dihydro-1*H*-imidazole-2-yl)-1*H*-indoles, which we have recently synthesized.[3]

Several methods for the formation of *C*-connected imidazolines have been described in the literature, which are mainly based on the reaction of compounds bearing nitriles,[4] esters[5] or carboxylic acids[6] with ethylenediamine (or salts there of) under various conditions with the corresponding imidazolines. However, the existing methods for the synthesis of the desired 3-(4,5-dihydro-1*H*-imidazole-2-yl)-1*H*-indoles with various substituents at the 2,4,5,6,7-position of the indole nucleus were less satisfactory in terms of availability of starting material, moderate yields, restricted generality and harsh conditions. In order to design a versatile and general approach, knowing that 1-acetyl-imidazolidin-2-one is a useful reagent for the direct formation of *N*-connected imidazolines by reaction with amines in the presence of $POCl_3$,[7] we chose to use this method for the synthesis of *C*-connected 3-(4,5-dihydro-1*H*-imidazole-2-yl)-1*H*-indoles.

Table 1. Formation of 2-methyl-3-(4,5-dihydro-1*H*-imidazole-2-yl)-1*H*-indoles

Entry	Starting indole	R1	R2	Product	Yield (%)[a]
1	**1a**	5-Cl	CH_3	**1**	62
2	**2a**	5-CF_3	CH_3	**2**	52
3	**3a**	5-Br	CH_3	**3**	80
4	**4a**	5-CH_3	CH_3	**4**	51
5	**5a**	5-OMe	CH_3	**5**	64
6	**6a**	H	CH_3	**6**	44

[a] Yields are not optimized.

Keywords: 3-(4,5-dihydro-1*H*-imidazole-2-yl)-1*H*-indoles; insulin secretagogues.

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0040-4039/01/$ - see front matter © 2001 Published by Elsevier Science Ltd.
PII: S0040-4039(01)00960-1

2. Chemistry

The preparation of the 3-(4,5-dihydro-1*H*-imidazole-2-yl)-indoles **1**–**16** (Tables 1 and 2) starting from the corresponding indoles with various substituents in different positions at the indole nucleus was carried out following the general route shown in Scheme 1.

For the first series of compounds we chose to use readily commercially available or synthesizable (via Fischer indole synthesis[8]) 2-methyl-1*H*-indoles with different substituents at the 5-position. Treatment of those indoles with commercially available 1-acetyl-imidazolidin-2-one in the presence of phosphorus oxychloride[9] gave in moderate to good yields the desired products (Table 1).

To further extend the scope of this method we focused on the synthesis of 3-(4,5-dihydro-1*H*-imidazole-2-yl)-1*H*-indoles with different substitution at the indole nucleus (Table 2).

Starting indoles **7a**–**14a** were made according to the Fischer indol synthesis.[8] It has to be noticed that the 6-chloro-2-methyl-1*H*-indole (entry 8) was obtained in a 1:1 mixture with the corresponding 4-chloro-2-methyl-1*H*-indole and was separated from this mixture by chromatography. Interestingly, the 2-unsubstituted indole **10a** gave according to the general procedure[9] a complex mixture of products and the desired product could not be detected. In this case more work is needed to optimize the reaction conditions in terms of temperature, dehydrating agent and using a different imidazolin-2-one derivative.

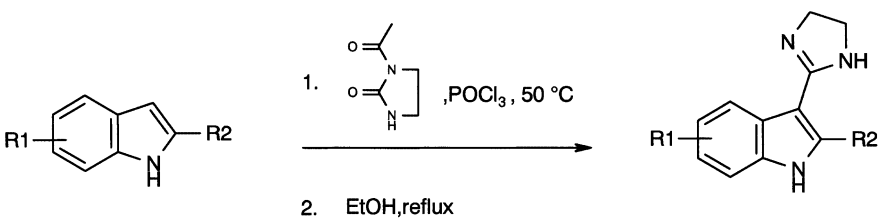
The starting indole **15a** (entry 15) was prepared in two steps (Scheme 2). The 5-chloro-1*H*-indole was treated with diphenyl disulfide as described in the general procedure by Atkinson et al.[10] and the resulting 5-chloro-3-phenylthio-1*H*-indole was isomerized in polyphosphoric acid into the corresponding 5-chloro-2-phenylthio-1*H*-indole as described by Hamel et al.[11] for the synthesis of 2-phenylthio-1*H*-indole in 67% yield.

Starting indole **16a** was prepared in a similar fashion. *N*-Benzylation of 5-chloro-1*H*-indole as described by Santaniello et al. for the parent indole,[12] followed by thermal isomerization in polyphosphoric acid led to 2-benzyl-5-chloro-1*H*-indole as described for 2-benzyl-1*H*-indole by Wiedenau et al.[13] in 60% yield (Scheme 3).[14]

Table 2. Formation of 3-(4,5-dihydro-1*H*-imidazole-2-yl)-1*H*-indoles

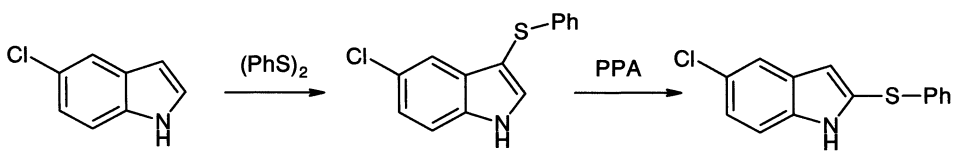
Entry	Starting indole	R1	R2	Product	Yield(%)[a]
7	**7a**	4-Cl	CH_3	**7**	56
8	**8a**	6-Cl	CH_3	**8**	60
9	**9a**	7-Br	CH_3	**9**	48
10	**10a**	5-Cl	H		0
11	**11a**	5-Cl	Et	**11**	67
12	**12a**	5-Cl	Cyclohexyl	**12**	59
13	**13a**	5-Cl	Phenyl	**13**	62
14	**14a**	5-Cl	4-Me-Phenyl	**14**	67
15	**15a**	5-Cl	Phenylthio	**15**	63
16	**16a**	5-Cl	Benzyl	**16**	61

[a] Yields are not optimized.



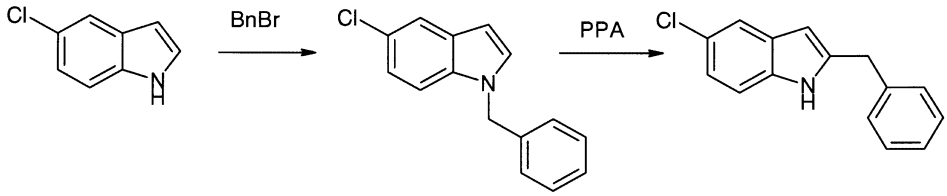
1a-16a **1-16**

Scheme 1.



15a

Scheme 2.



16a

Scheme 3.

3. Conclusion

In summary we described a new method for the formation of at the indole nucleus substituted 3-(4,5-dihydro-1*H*-imidazole-2-yl)-1*H*-indoles starting from various 1*H*-indoles in a one-pot reaction. This approach provides significant advantages over the existing methods in terms of yields, reaction conditions and effectiveness, especially if the target molecule is substituted in the 4-, 5-, 6- or 7-position.

Acknowledgements

The authors would like to thank Dr. Andreas Weichert and Dr. Chuan Shih for helpful discussions.

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9. General procedure for the synthesis of 3-(4,5-dihydro-1*H*-imidazole-2-yl)-1*H*-indoles:
   A mixture of indole (10 mmol) and 1-acetyl-imidazolidine-2-one (11 mmol) was added to phosphorus oxychloride (8 ml) and heated to 50°C. After 3–5 h, phosphorus oxychloride was evaporated. The residue was treated with ethanol (10 ml) cautiously and maintained at reflux for 2–3 h. The mixture was concentrated under reduced pressure to half of the volume to obtain a precipitate, which was collected by filtration. The crystalline residue was treated with water, washed with ethyl acetate and dried in vacuo.
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14. All new compounds show analytical and spectra (^{1}H NMR) data consistent with the depicted structure.