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A novel and convenient route for the construction of 5-((1*H*-1,2,4-triazol-1-yl)methyl)-1*H*-indoles and its application in the synthesis of Rizatriptan

Yi He †, Xiaolong Li †, Jue Li, Xiaocen Li, Li Guo, Li Hai *, Yong Wu *

Key Laboratory of Drug-Targeting of Education Ministry and Department of Medicinal Chemistry, West China School of Pharmacy, Sichuan University, Chengdu 610041, PR China

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ABSTRACT

In this study, a novel and convenient route for the construction of 5-((1*H*-1,2,4-triazol-1-yl)methyl)-1*H*-indoles (**8**) is presented starting from (1*H*-1,2,4-triazol-1-yl)methanol (**5**) and indolines (**6**) under 98% H_2SO_4 at room temperature for 4–24 h, followed by deacetylation and dehydrogenation. Based on this finding, a novel route to synthesize Rizatriptan starting from tryptamine was designed and accomplished with 48.5% overall yield in 6 steps. Compared with operational art, the new route afforded higher yield and more pure products requiring no chromatographic purification, which may further be applied in industrialization.

Indole and its derivatives are very important physiologically active substances which are widely distributed in nature. Chemicals with the indole structure are also important heterocyclic intermediates for the synthesis of agrochemicals, pharmaceuticals, and finechemicals.[1] Meanwhile, 1,2,4-triazols constitute an important class of heterocyclic nitrogen derivatives showing various biological activities such as herbicides, defoliants, growth regulators, fungicides, and insecticides.[2] Ploya reported 3-amino-1,2,4-triazole's application as the neutral herbicide and defoliant of cotton.[2] Scalzo et al. described the antimycotic activity of (1*H*-1,2,4-triazol-1-ylmethyl)aniline derivatives.[3] EI-Zemity et al. also synthesized a series of (1*H*-1,2,4-triazol-1-ylmethyl)aniline derivatives, showing good potency in molluscicidal activity.[4] The fusion of these two structures gave out a family of tryptamine-based drugs, containing 5-(1*H*-1,2,4-triazol-1-yl)methyl substituted indoles (Fig. 1, **I**) certified to be the effective 5-$HT_{1B/1D}$ receptor agonists which can be used in the treatment of migraine and associated conditions.[5] Rizatriptan is a triptan drug for the treatment of migraine headaches, which has been on market in the form of benzoate since 1998.

However, preparations of 5-(1*H*-1,2,4-triazol-1-yl)methyl substituted indoles (**I**) are limited. In the synthesis of Rizatriptan, construction of the indole structure was realized mainly via two methods: Fisher indole reaction and palladium-catalyzed coupling ring closure reaction (Scheme 1). Previously, Houghton[6] described a process starting from 4-((1*H*-1,2,4-triazol-1-yl)methyl)aniline (**1**) and the hydrazine intermediate(**2**) experienced Fisher indole reaction with 4,4-dimethoxy-*N*,*N*-dimethylbutan-1-amine to construct the substituted indole ring structure to make Rizatriptan (Scheme 1, route a, operational route). Baker et al.[5] also described a homothetic route in earlier time. The construction of the indole structure was achieved via Fisher indole reaction in 5 N HCl at reflux for 4 h, which provided a lot of byproducts with low yield (38% yield for single step of construction of the indole structure[5a]).

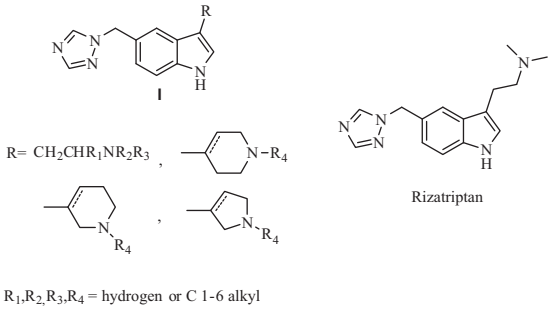

Figure 1. Structure of 5-(1*H*-1,2,4-triazol-1-yl)methyl substituted indoles (**I**) and Rizatriptan.

* Corresponding authors. Tel.: +86 02885503235; fax: +86 02885503666 (L.H.); tel./fax: +86 02885503666 (Y.W.).
E-mail addresses: smile@scu.edu.cn (L. Hai), wyong@scu.edu.cn (Y. Wu).
† Yi He and Xiaolong Li are co-first authors.

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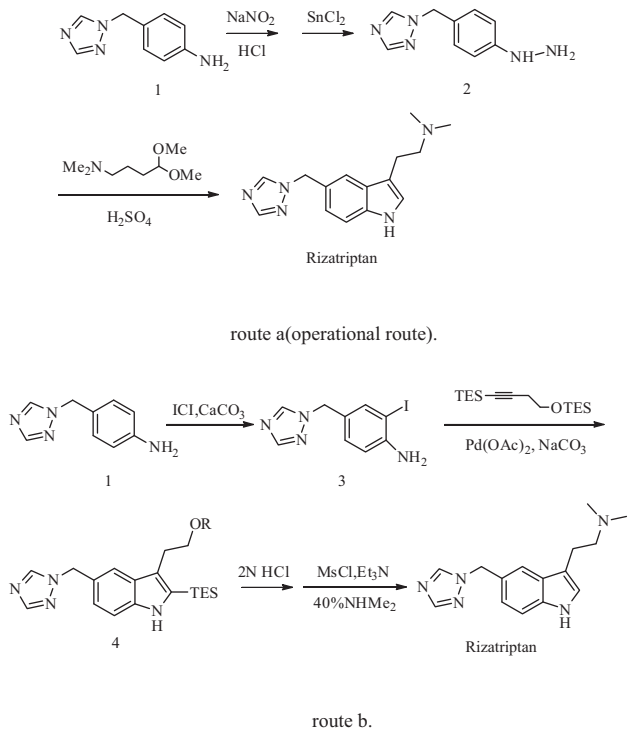
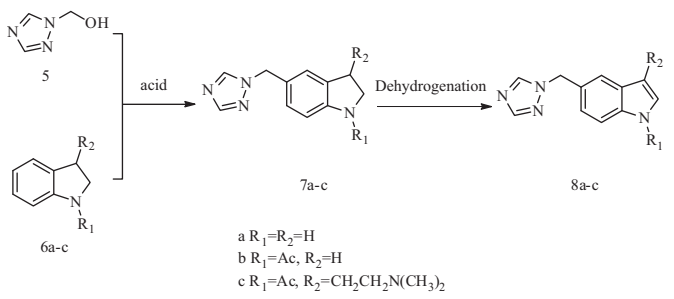


Scheme 1. Two main routes to prepare Rizatriptan.

The purification of the final product was very tough and column chromatography had to be adopted, leading to very low total yield of 11.1%.[5a] Houghton[6] later improved total yield to 45% but column chromatography was used in purification with high cost. Cheng Y. Chen et al.[7] represented a process to prepare Rizatriptan, by palladium-catalyzed coupling ring closure of 3-iodine-4-aminobenzyltriazol (**3**) with bis-TES-butynol to the corresponding tryptophol intermediate (**4**) (Scheme 1, route b). This process was catalyzed by palladium acetate in dry dimethylformamide in the presence of Na_2CO_3 at 100 °C for 4 h. The palladium catalyst is expensive, and the quite strict oxygen-free and anhydrous conditions need high-level equipment requirement, complexing the operation and increasing the costs. Also *n*-BuLi was used in preparing bis-TES-butynol in this route, which is often eluded in industrial production. Most of other reported routes were similar to the two routes above. Obviously, neither Fisher indole reaction nor palladium-catalyzed coupling reaction could meet the demand for high purity and yield in the preparation of Rizatriptan. We herein report a new method to prepare **I** starting from (1*H*-1,2,4-triazol-1-yl)methanol (**5**) and indolines (**6**).

Katritzky et al.[8] published a method to provide (1*H*-1,2,4-triazol-1-yl)methyl substituted phenols, anilines, *N*-alkylanilines, and *N*,*N*-dialkylanilines by triazolylalkylating the substrates with (1*H*-1,2,4-triazol-1-yl)methanol (**5**) in the presence of 37% HCl or CH_3COOH. In particular, when the substrates are anilines, *N*-alkylanilines, and *N*,*N*-dialkylanilines, the substitution happened on the *para*-position. Inspired by this and for application in preparing Rizatriptan, we tried 5-(1*H*-1,2,4-triazol-1-yl)methylation of indolines (**6**) under the condition of 37% HCl or CH_3COOH, hoping to get 5-((1*H*-1,2,4-triazol-1-yl)methyl)indulines (**7**) as the main product, which could be further dehydrogenated to yield the 5-(1*H*-1,2,4-triazol-1-yl)methyl substituted indoles (**8**) (Scheme 2). As the dehydrogenation of compounds with the indoline structure has been abundantly explored[9] and realized very successfully by us later, our work mainly focused on the preparation of key intermediate **7**.



Scheme 2. A novel construction of 5-((1*H*-1,2,4-triazol-1-yl)methyl substituted indoles (**8**).

As a model reaction, **6a** was first adopted as the substrate to react with **5** under literature conditions.[8] Disappointedly, as shown in Table 1, no 5-((1*H*-1,2,4-triazol-1-yl)methyl)indoline (**7a**) was found under the condition of neither 37% HCl nor CH_3COOH (Table 1, entries 1 and 2). Contrarily, acetylated 5-((1*H*-1,2,4-triazol-1-yl)methyl)indoline (**7b**) was obtained as the main product under the condition of CH_3COOH in a poor yield of 11% (Table 1, entry 2).

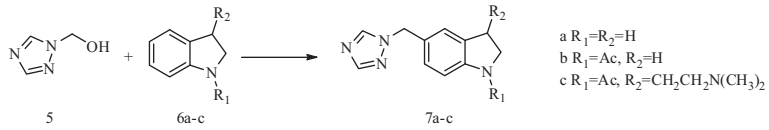
Considering the different results described in the literature,[8] we supposed that **7b** with 1-N acetylated might be more stable than **7a** under the reaction condition. This may result from the electron-withdrawing effect of acetyl, which makes the electron density of benzylic carbon of **7b** lower than that of **7a**, declining the leave-taking of the triazol under strong acid environment which could cause the degradation of the product described by Katritzky et al.[8,10]

So we then chose 1-(indolin-1-yl)ethanone (**6b**) as the substrate to screen the best triazolylalkylating condition in the presence of varying proton or Lewis acids. The reaction was monitored by TLC and the results are shown in Table 1. Firstly 37% HCl and CH_3COOH were tried as the literature procedure.[8] And to ensure the exhaustion of **6b**, the reactant ratio (**5**:**6b**) was added to 1.5 (Table 1, entry 3 and 4). Unfortunately, only trace amount of **7b** were found. We then applied several classic Friedel–Crafts acylation conditions, utilizing Lewis acids such as $AlCl_3$, $ZnCl_2$, and resin in the solvent of nitrobenzene under 80 °C (Table 1, entries 5–7). But no product was formed. Then lower concentrations of acids such as 15% HCl, 20% and 50% H_2SO_4 (Table 1, entries 8–10) were used. There was no desired product, which suggested that too much water might be negative to the reaction. Therefore, organic acids such as HCOOH, CF_3COOH, and CF_3SO_3H (Table 1, entries 11–13) were also tried. When CF_3SO_3H was tried, **7b** was generated in 6% yield. Encouraged by this result, we then tested some other strong acids with dehydration such as PPA and 98% H_2SO_4 (Table 1, entries 14–15), getting **7b** in 13% and 16% yield. The positive performance of PPA and 98% H_2SO_4 might be the dehydration property of them that can facilitate the ionization of the triazole methanol to smooth the reaction (Scheme 3).

As PPA is very viscous and difficult to stir at low temperature, we focused on the conditions using 98% H_2SO_4 to optimize the reaction condition. Different temperature and reactant ratios (Table 1, entries 16–21) were tested. Even though the yield was the most optimal with a ratio of 1.5 at 25 °C for 24 h (Table 1, entry 18), it was still very low and not enough in application.

Considering that the introduction of side chain may make the product more stable and applied in the synthesis of Rizatriptan, we attempted to choose **6c** as the substrate to react with **5**, expecting the high yield of **7c** under specific conditions. Similarly with **6b**, only CF_3SO_3H, PPA, and 98% H_2SO_4 generated the usable amount of product (Table 1, entries 22–24). Encouragingly, the yields of those were respectively higher than that of **6b**, which revealed that the introduction of side chain was indeed positive to the reaction. Then

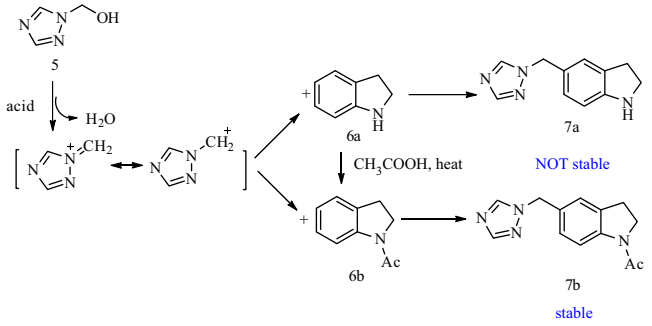
Table 1
Optimization of reaction conditions for the synthesis of **7**



5 6a-c 7a-c

Entry	Indolines	Acid[a]	Reactant ratio (5:6)	Temp (°C)	Time[b] (h)	Product	Yield[c] (%)
1	**6a**	37% HCl	1	Reflux	7	—	0
2	**6a**	CH_3COOH	1	Reflux	7	**7b**	11
3	**6b**	37% HCl	1.5	Reflux	7	**7b**	Trace
4	**6b**	CH_3COOH	1.5	Reflux	7	**7b**	Trace
5	**6b**	$AlCl_3$	1.5	80	7	—	0
6	**6b**	$ZnCl_2$	1.5	80	7	—	0
7	**6b**	Resin	1.5	80	7	—	0
8	**6b**	15% HCl	1.5	80	7	—	0
9	**6b**	20% H_2SO_4	1.5	80	7	—	0
10	**6b**	50% H_2SO_4	1.5	80	7	—	0
11	**6b**	HCOOH	1.5	80	7	**7b**	Trace
12	**6b**	CF_3COOH	1.5	80	7	**7b**	Trace
13	**6b**	CF_3SO_3H	1.5	80	7	**7b**	6
14	**6b**	PPA	1.5	80	7	**7b**	13
15	**6b**	98% H_2SO_4	1.5	80	7	**7b**	16
16	**6b**	98% H_2SO_4	1.5	80	3	**7b**	10
17	**6b**	98% H_2SO_4	1.5	50	12	**7b**	22
18	**6b**	98% H_2SO_4	1.5	25	24	**7b**	24
19	**6b**	98% H_2SO_4	1.2	25	24	**7b**	15
20	**6b**	98% H_2SO_4	0.5	25	36	**7b**	8
21	**6b**	98% H_2SO_4	5	25	18	**7b**	18
22	**6c**	CF_3SO_3H	1.5	80	7	**7c**	16
23	**6c**	PPA	1.5	80	7	**7c**	23
24	**6c**	98% H_2SO_4	1.5	80	2	**7c**	33
25	**6c**	98% H_2SO_4	1.5	25	4	**7c**	71

[a] Typical procedure: in entries 1–4; 8–25: 1 mmol **6**, *n* mmol **5**, 1 ml acid; in entries 5–7: 1 mmol **6**, 1.5 mmol **5**, 1 mmol Lewis acid, 1 ml nitrobenzene.
[b] Complete reaction time of substrates.
[c] Isolated yield by column chromatography.

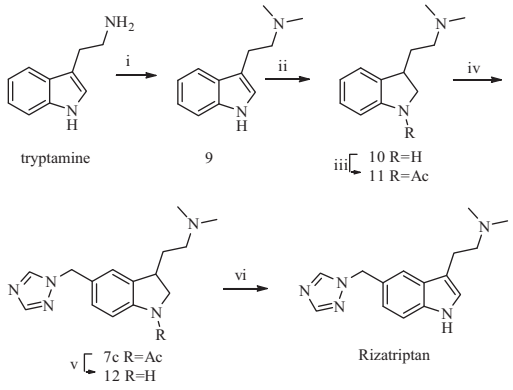


Scheme 3. Mechanism of the 5-(1*H*-1,2,4-triazol-1-yl)methylation of indolines.

the reaction time, temperature, and reactant ratio were screened, and finally, the yield was improved to 71% when the reaction was conducted at 25 °C for only 4 h at the reactant ratio of 1.5 (Table 1, entry 25).

As the deacetylation and dehydrogenation were later proved with high yield successfully by using 40% NaOH and DDQ, this mild condition was sufficient enough for application, compared to that of fisher indole reaction (38% yield for single step) in the operational art. And purification of **7c** can be easily obtained via recrystallization in ethyl acetate–hexane (4:1), requiring no chromatographic purification.

Based on the results above, a novel route to synthesize Rizatriptan was achieved from tryptamine as outlined in Scheme 4. In brief, tryptamine first underwent reductive amination with HCHO and $NaBH_4$[11] to afford **9**, which was then reduced by Et_3SiH in CF_3COOH[12] to provide **10**. After acetylation, **11** then reacted with (1*H*-1,2,4-triazol-1-yl)methanol (**5**) in 98% H_2SO_4 at room temperature for 4 h to produce the key intermediate **7c** in 71% yield after recrystallization with ethyl acetate–hexane (4:1). **7c** was further deacetylated by 40% NaOH, to form **12**, and after dehydrogenation with DDQ[9b] in toluene the product was obtained, which was then recrystallized in ethyl acetate to produce high purity Rizatriptan. In this route, the raw material tryptamine is a biological metabolite which is commercially available, making the scale production of Rizatriptan by this route feasible. Moreover the key step reaction to form **7c** is under mild conditions without catalysts, and other



Scheme 4. A novel route to synthesize Rizatriptan. Reagents and conditions: (i) HCHO/MeOH, $NaBH_4/H_2O$, MeOH, 5–15 °C, 90.2%; (ii) Et_3SiH, CF_3COOH, 50 °C 16 h, 94.1%; (iii) CH_3COCl, CH_3COOH, 90 °C 2 h, 100%; (iv) (1*H*-1,2,4-triazol-1-yl)methanol, 98% H_2SO_4, rt 4 h, 71.2%; (v) 40%NaOH, MeOH, 80 °C 1.5 h, 96.3%; (vi) DDQ, toluene, reflux overnight, 83.4%.

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steps are simple reactions like acetylation–deacetylation, oxidation-reduction with nearly quantitative yield. A laboratory scale of this route has been accomplished with 48.5% overall yield from tryptamine in 6 steps without chromatographic purification. The properties (mp, ^{1}H and ^{13}C NMR, MS, elemental analysis given in Supplementary material) of Rizatriptan made by this route identical to that of operational art.[5,6]

In conclusion, we provide a novel route for the construction of 5-((1*H*-1,2,4-triazol-1-yl)methyl)-1*H*-indoles (**8**), starting from (1*H*-1,2,4-triazol-1-yl)methanol (**5**) and indolines (**6**) in 98% H_2SO_4 at room temperature for 4–24 h to get the key intermediate **7**, followed by deacetylation and dehydrogenation. The construction of the indole structure is under mild condition with higher yield than that of Fisher indole synthesis in the operational art, also with an easier progress in purification. Based on this finding, a novel route to synthesize Rizatriptan starting from tryptamine with 48.5% overall yield in 6 steps is designed and accomplished. Further study of industrialization of the new route is still ongoing.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.05.063.

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