Pergamon

Tetrahedron Letters 43 (2002) 2407–2409

TETRAHEDRON LETTERS

Synthesis of huperzine intermediates via Mn(III)-mediated radical cyclization

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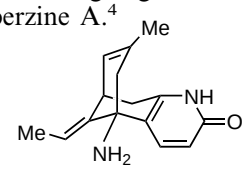
Received 10 December 2001; revised 5 February 2002; accepted 8 February 2002

Abstract—Key intermediates of huperzine were obtained via Mn(III)-mediated oxidative radical cyclization of allylic derivatives from 6-oxotetrahydroquinoline carboxylic esters to the corresponding bicyclic compounds. © 2002 Published by Elsevier Science Ltd.

Huperzine A (**1**), isolated from the clubmoss *Huperzia serrata* (*Yhunb.*)[1] Trev. = *Lycopodium serratum Thunb.*, is a potent, selective, reversible inhibitor of acetylcholinesterase (AchE),[2] and is presently under clinical trials as treatment for Alzheimer's disease.[2,3] As an AchE inhibitor, huperzine A is superior to tacrine because of its high therapeutic index and longer duration of action. This particular biological activity has stimulated efforts among organic chemists towards the synthesis of huperzine A.[4]

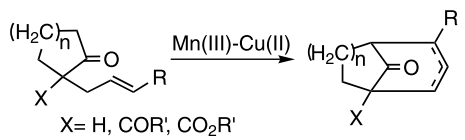


Huperzine A (1)

Generally, most cyclization reactions toward the bicyclic skeleton of huperzine A can be performed by reactions such as the tandem Michael addition–intramolecular adol condensation upon the β-keto esters with α,β-unsaturated aldehydes[4b] or palladium-catalyzed bicycloannulation reaction of the β-keto esters with methallyl diacetate.[5]

As for the reported Mn(III)-mediated oxidative radical cyclization, Snider et al. reported its application to the synthesis of cyclic compounds from unsaturated ketones, 1,3-diketones, β-keto esters[6] (Eq. (1)). White and Jeffrey described a possible application of the methodology to the construction of huperzine A. So far, the utilization of this reaction toward huperzine A has not been reported in the literature.[7]

In our synthetic plan, we adopted Mn(III)-mediated oxidative radical cyclization for the introduction of the bicyclic bridge of huperzine A and its analogs.



(1)

We envisioned the synthesis of huperzine and its analogs can be brought about by the utilization of this Mn(III)-mediated reaction (Eq. (2)).

The precursor of the cyclic β-keto ester with an aromatic ring for the oxidative radical cyclization was prepared by the following reaction. The deprotonation of cyclic β-keto ester **2** using NaH/DMF at room temperature followed by alkylation with the corresponding alkyl bromides provided allylic derivatives **3**. Reaction of **3** to the corresponding bicyclic compound **4** was performed by the treatment of 0.1 M solution of **3** in acetic acid with 2.5 equiv. of $Mn(OAc)_3 \cdot 2H_2O$ and 1 equiv. of $Cu(OAc)_2 \cdot H_2O$ for overnight at 60–80°C to

Keywords: huperzine; radical cyclization; acetylcholinesterase (AchE) inhibitor.

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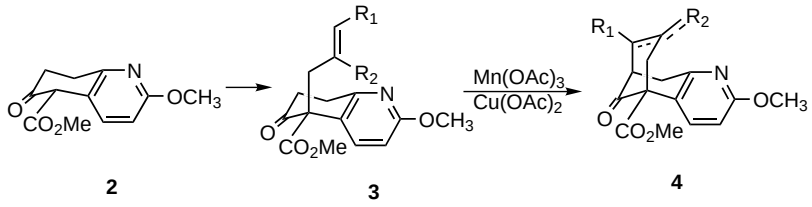
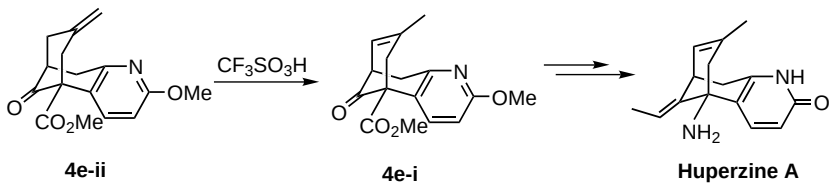
0040-4039/02/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0040-4039(02)00270-8



(2)

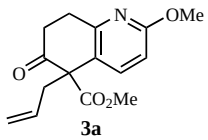
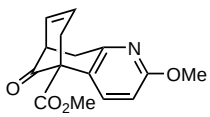
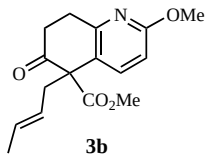
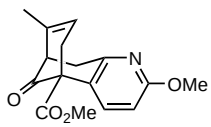
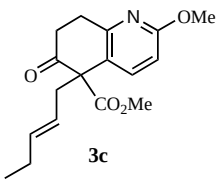
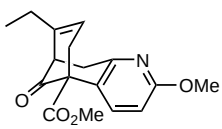
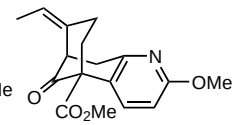
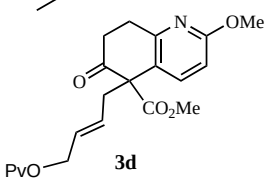
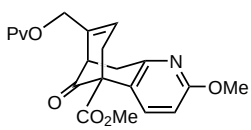
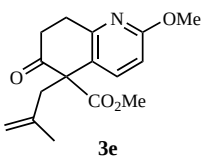
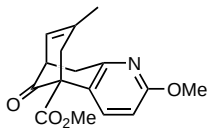
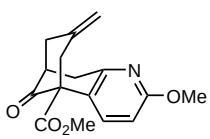
afford bicyclic compounds. Results are shown in Table 1. Most allylic β-keto esters gave the endocyclic products, which are thermodynamically more stable than exodocyclic products. An exception is entry 5 that produced more of the exocyclic product. We found that control of the inner temperature of the reactions is very critical. For example, in the case of a compound with a pivaloyl group (entry 4), the reaction was very slow under standard conditions (70°C, 60 h) and some of the starting material was recovered. However, at the slightly higher temperature of 80°C, the reaction became fast, but the obtained yields were low because of formation of unwanted byproducts.

Thermodynamically unstable *exo* cyclization product **4e–ii** of the huperzine intermediate was easily isomerized to the endocyclic compound **4e–i** by treating it with triflic acid.(Eq. (3)) The combined compound **4e–i** was successively converted into huperzine A by the known literature procedure.[4d]



(3)

Table 1. Mn(III)-mediated oxidative radical cyclization of cyclic β-keto esters

Entry	β-Keto Esters	Reaction Temperature	Products (Yields)
1	 **3a**	80 °C	 **4a** (84%)
2	 **3b**	60 °C	 **4b** (72%)
3	 **3c**	70 °C	 **4c-i** (61%)  **4c-ii** (5%)
4	 **3d**	70 °C	 **4d** (32%)
5	 **3e**	60 °C	 **4e-i** (21%)  **4e-ii** (40%)

Acknowledgements

This work was supported by the Ministry of Science and Technology Grant (KK-0103-B0) and Kolon Central Research Institute.

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