Chinese Chemical Letters 24 (2013) 347–350

Contents lists available at SciVerse ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Original article

An efficient synthesis of 2,3-diaryl-2-azabicyclo[2.2.2]octan-5-ones and their acetylcholinesterase inhibitory activity

Li Huang, Jun-Pei Chen, Can Jin, Wei-Ke Su *

Key Laboratory for Green Pharmaceutical Technologies and Related Equipment of Ministry of Education, College of Pharmaceutical Sciences, Zhejiang University of Technology, Hangzhou 310014, China

ARTICLE INFO

Article history:
Received 23 November 2012
Available online xxx
Received in revised form 8 January 2013
Accepted 11 January 2013
Available online 7 March 2013

Keywords:
Aza-Diels–Alder cycloaddition
Azabicyclo[2.2.2]octan-5-one
Sodium calix[4]arene sulfonate
α-ZrP
AChE inhibition

ABSTRACT

A series of substituted 2,3-diaryl-2-azabicyclo[2.2.2]octan-5-ones have been prepared by an efficient three-component aza-Diels–Alder cycloaddition reaction in water catalyzed by layered α-zirconium hydrogen phosphate (α-ZrP) and sodium calix[4]arene sulfonates bearing pendant short aliphatic chains. The 18 synthesized compounds were assayed for acetylcholinesterase inhibition using mouse acetylcholinesterase.

1. Introduction

Azabicyclo[2.2.2]octane derivatives have attracted great attention due to their important pharmacological roles and have been reported to be agonists of α7 nicotinic acetylcholine receptors [1], antagonists of CCR3 [2], antiparasitics [3], antimalarial and antileishmanial agents [4], and AChE inhibitors [5]. The aza-Diels–Alder cycloaddition reaction of imines with electron-rich dienophiles represents an important contribution to the synthesis of such compounds, which could be catalyzed by Lewis or Brønsted acid, such as $BiCl_3$ [6], BF_3-OEt_2 [7], trifluoroacetic acid [8], α-zirconium phosphate (α-ZrP) [9], triphenylphosphonium perchlorate (TPP) [10] and silicotungstic acid [5]. The catalysts of some asymmetric aza-Diels–Alder reactions appeared in recent years included L-proline [11], [Emim][Pro] [12], *p*-dodecylphenylsulfonamide [13], 1-(2-hydroxynaphthalen-1-yl)naphthalen-2-ol (BINOL) derived phosphoric Brønsted acids [14], a mixture of acetic acid and BINOL-derived phosphoric Brønsted acids [15] and so on. However, these procedures suffer from the disadvantages of using expensive reagents, long reaction time, and low yields, and several Lewis acids could not be reused. Based on sodium calix[4]arene sulfonates bearing pendant aliphatic chains [16] (**1a**, **1b** and **1c** shown in Fig. 1) with hydrophobic alkyl, aryl groups and a cavity that plays the role of extraction [17,18], we assumed that the use of these calix[4]arene derivatives as surfactant-type catalysts could enhance the efficiency of catalytic aza-Diels–Alder cycloaddition in water and be helpful to overcome the problem of low regioselectivity. Herein, we described an efficient method for the synthesis of azabicyclo[2.2.2]octan-5-ones using catalytic amounts of α-ZrP and sodium calix[4]arene sulfonates bearing pendant aliphatic chains under mild reaction conditions in high yields and good regioselectivity.

2. Experimental

Analytical grade solvents and commercially available reagents were used without further purification. Doubly distilled water was used as solvent for the aza-Diels–Alder reaction. Microwave irradiation experiments were carried out in a Discover-CEM mono mode microwave apparatus. The flash column chromatography was carried out using silica gel (200–400 mesh), purchased from Qingdao Haiyang Chemical Co., Ltd. Melting points were determined on a Buchi B-540 capillary melting point apparatus and uncorrected. Mass spectra were recorded on a Finnigan LCQ-Advantage. The NMR spectra were obtained on a Varian-400 instrument (^{1}H NMR at 400 MHz, ^{13}C NMR at 100 MHz) using $CDCl_3$, D_2O or DMSO-d_6 as the solvent and TMS as an internal standard. Chemical shifts are given relative to TMS, the coupling constants *J* are given in Hertz. IR spectra were recorded using KBr

* Corresponding author.
E-mail address: pharmlab@zjut.edu.cn (W.-K. Su).

1001-8417/$ – see front matter © 2013 Wei-Ke Su. Published by Elsevier B.V. on behalf of Chinese Chemical Society. All rights reserved.
http://dx.doi.org/10.1016/j.cclet.2013.01.045

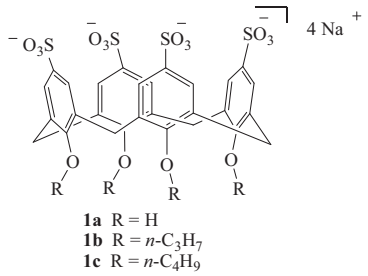


Fig. 1. The surfactant-type catalyst of calix[4]arene sodium sulfonate bearing pendant aliphatic chains (**1a**, **1b** and **1c**).

pellets on a Nicolet Aviatar-370 instrument. High resolution mass spectral (HRMS) analysis was measured on a Bruker micrOTOF-Q II using ESI techniques. The *exo*/*endo* ratio was determined by HPLC (Agilent 1200) analyses and ^{1}H NMR. Layered α-zirconium hydrogen phosphate (α-ZrP) was prepared as reported in the literature [19]. The sodium calix[4]arene sulfonates bearing pendant aliphatic chains (**1a**, **1b**, and **1c**) were prepared as reported in the literature [16].

Typical procedure for aza-Diels–Alder reaction: Aromatic aldehyde (**4a**, 0.5 mmol), aromatic amine (**3a**, 0.6 mmol), cyclohexenone (**2**, 5 mmol), catalyst α-ZrP (0.01 mmol), **1c** (0.005 mmol) and H_2O (1 mL) were added to a 2 mL vial. The mixture was stirred at 30 °C for 24 h (Table 2). The reaction mixture was extracted with ethyl acetate (3 × 2 mL). The organic phase was separated from the aqueous medium by centrifugation, and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to produce a residue, which was purified by column chromatography (silica gel, hexanes/ethyl acetate = 45:1) to afford **5a** (46 mg, 30%) and **6a** (79 mg, 52%), respectively (Scheme 1). Spectral data for obtained compounds please see supporting information.

General procedure for recycling the catalyst (α-ZrP and **1c***):* After the aza-Diels–Alder reaction completed, the reaction mixture was extracted with ethyl acetate (3 × 2 mL), then, two phases were separated further by centrifugation. The organic phase was collected using a syringe, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude products (**5** and **6**) were purified by column chromatography. The catalyst system (α-ZrP and **1c**) of the aqueous phase was reused in the next cycle of aqueous reactions directly (Scheme 2).

Table 1
Aza-Diels–Alder reaction of 2-cyclohexen-1-one (**2**) with 4-methoxyaniline (**3a**) and benzaldehyde (**4a**).[a]

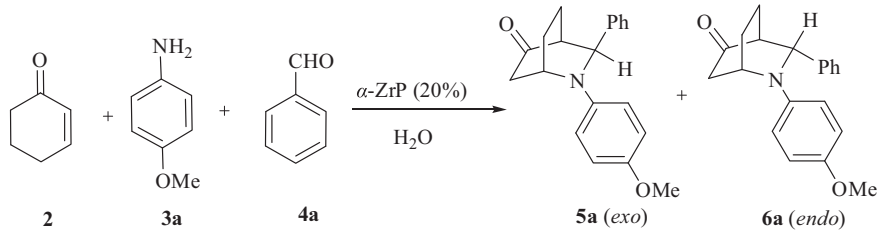
Entry	Additive (equiv.)	Yield (**5a** + **6a**) (%)[b]	Ratio of **5a**/**6a**[c]
1	**1a** (5 mol%)	50	36:64
2	**1b** (5 mol%)	66	38:62
3	**1c** (5 mol%)	70	35:65
4	**1c** (10 mol%)	82, 81[d], 80[e], 80[f]	37:63, 37:63[d], 38:62[e], 37:63[f]
5	**1c** (20 mol%)	82	36:64
6	**1c** (10 mol%)	7[g]	38:6[g]
7	**1c** (10 mol%)	2[h]	37:6[h]

[a] Reaction conditions: aldehyde (**4a**, 0.5 mmol), amine (**3a**, 0.6 mmol), cyclohexenone (**2**, 5 mmol), at 30 °C for 24 h, unless specified otherwise.
[b] Isolated yield based on **4a**.
[c] Determined by HPLC and NMR.
[d] The catalytic system was recycled for first time.
[e] The catalytic system was recycled for second time.
[f] The catalytic system was recycled for third time.
[g] Cyclohexenone (**2**, 5 equiv.).
[h] Under microwave radiation for 140 °C, 10 min.

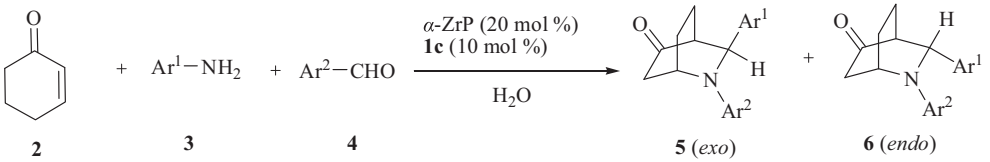
3. Results and discussion

Initially, we investigated the influence of catalysts on the reaction (Table 1). It was shown that the pendant aliphatic chains of the catalysts affected their activity. The corresponding products (70%) were obtained in the presence of α-ZrP (20 mol%) under **1c** (5 mol%), compared to 66% under **1b** and 50% under **1a** (Table 1, entries 1–3). The amount of **1c** also had an impact on the reaction. Increasing the amount of **1c** to 10 mol% (Table 1, entry 4) produced a mixture of products **5a** and **6a** with an *exo*(**5a**)/*endo*(**6a**) ratio of 37:63 in 82% combined yield. But increasing the amount of **1c** to 20 mol% would not improve the yield further (Table 1, entry 5). Disappointedly, low product yield was obtained when this protocol was applied under microwave radiation (Table 1, entry 7). It was illustrated that the high reaction temperature was not propitious to form nitrogen-containing heterocycles, producing several side-products. The best result was achieved when the reaction was catalyzed by 10 mol% of **1c** and 20 mol% of α-ZrP in water at 30 °C for 24 h.

Inspired by these results, we investigated the scope of the reaction using a series of aryl amines **3** and various aryl aldehydes **4**. To our delight, the aza-Diels–Alder cycloaddition of benzaldehyde and cyclohexenone combined with a broad range of aryl amines bearing electron-donating or electron-withdrawing



Scheme 1. Synthesis of 2-(4-methoxyphenyl)-3-phenyl-2-azabicyclo[2.2.2]octan-5-one (**5a** + **6a**) *via* the aza-Diels–Alder cycloaddition.



Scheme 2. Synthesis of 2,3-diaryl-2-azabicyclo[2.2.2]octan-5-ones (**5** + **6**) *via* the aza-Diels–Alder cycloaddition.