Tetrahedron xxx (2017) 1–6

Contents lists available at ScienceDirect

Tetrahedron

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

A mild and one-step synthesis of 2,8-dioxabicyclo [3.3.1] nonane derivatives via classical Knoevenagel condensation

De-Suo Yang*, Sen Ke, Xin Du, Peng Gao, Hai-Tao Zhu, Ming-Jin Fan**

Shaanxi Key Laboratory of Phytochemistry, College of Chemistry and Chemical Engineering, Baoji University of Arts and Sciences, Baoji, 721013, China

ARTICLE INFO

Article history:
Received 22 May 2017
Received in revised form
26 July 2017
Accepted 28 July 2017
Available online xxx

Keywords:
2,8-Dioxabicyclo [3.3.1] nonane
Knoevenagel condensation
V-shaped rigid framework

ABSTRACT

Utilizing simple and readily available 2-hydroxy benzaldehydes and 1,3-diketones or 1,3-cyclohexanediones as raw materials, complex 2,8-dioxabicyclo [3.3.1] nonane derivatives were synthesized in one-step via classical Knoevenagel condensation. The reaction was simply conducted under solvent-free and mild conditions, which showed good tolerance to a variety of functional groups. This atom-economical approach delivers an attractive synthetic protocol for 2,8-dioxabicyclo [3.3.1] nonane derivatives.

1. Introduction

2,8-Dioxabicyclo [3.3.1] nonane skeletons are precious in natural compounds because of their elaborate V-shaped rigid frameworks and structural complexities.[1] These skeletons have been shown to possess a number of biological and pharmacological activities.[2,3] For example, the flavonoid proanthocyanidin A1 and A2,[4] dracoflavan C and D,[5] ephedrannin A and B,[6] diinsininol (5) and (4) isolated from natural compounds,[7] all exhibit a wide range of biological and pharmacological properties including anti-inflammatory,[8] antimicrobial,[9] antiviral activities,[10] anticoagulant and so on (Fig. 1). Therefore, they have drawn enormous attention and stimulated organic chemists to design strategies for assembling these challenging structures in recent years.[11–13] Manolov and coworkers illustrated a base-catalyzed condensation between 3-benzoylcoumarin and 4-hydroxycoumarin to afford the corresponding 1-phenyl 2,8-dioxabicyclo [3.3.1] nonanes.[14] Yang reported that these molecules could be achieved through the reaction of 2-phenylchroman-4-ol with 4-hydroxycoumarin in the presence of aluminum chloride.[15] Wu and Ganguly described the synthesis of 2,8-dioxabicyclo [3.3.1] nonanes derivatives from 2-hydroxychalcone-α,β-enones and 4-hydroxycoumarin respectively.[16] Aldehyde-substituted vinylogous carbonates and 1,3-diketones/1,3-cyclohexanediones could also be used as raw materials to construct 2,8-dioxabicyclo [3.3.1] nonane derivatives via cascade Knoevenagel/hetero-Dielse-Alder reactions catalyzed by $AuBr_3$ and D-proline.[17] In fact, all these strategies possess shortcomings of harsh reaction conditions, expensive catalysts or complicated starting materials. The development of efficient and metal free catalytic methods toward 2,8-dioxabicyclo [3.3.1] nonanes from simple starting materials is still of significant interest and also represents one of the most challenging goals in organic synthesis.[18]

As we all know that benzaldehyde can react with 1,3-diketones to afford condensation products in the presence of piperidine/acetic acid and this reaction was called Knoevenagel condensation reaction. It is a versatile, convenient and extensively used reaction, which represents one of the most fundamental bond-forming protocol in organic synthesis.[19] However, during our research, we are surprised to find that 2,8-dioxabicyclo [3.3.1] nonanes can be produced by the reaction of 2-hydroxybenzaldehyde with 1,3-diketones under classical Knoevenagel condensation conditions. Herein, we report this efficient synthesis of diverse 1-aryl-substituted 2,8-dioxabicyclo [3.3.1] nonane derivatives from cheap 2-hydroxybenzaldehyde and 1,3-diketones.

2. Results and discussion

For the initial feasibility studies, 2-hydroxybenzaldehyde (**1a**) and 2,4-pentanedione (**2a**) were selected as model substrates to study the cycloaddition. **1a** (1 mmol) and **2a** (2.0 mmol) were

* Corresponding author.
** Corresponding author.
E-mail address: yangdesuo@163.com (D.-S. Yang).

http://dx.doi.org/10.1016/j.tet.2017.07.054
0040-4020/

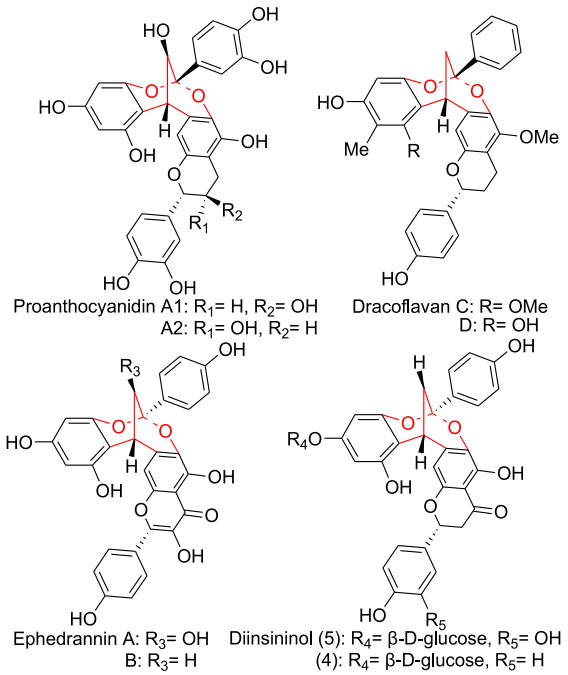
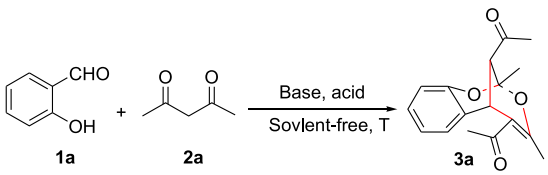


Fig. 1. Biologically interesting natural products containing 2,8-dioxabicyclo [3.3.1] non-3-ene skeleton.

treated with piperidine (0.6 eq.) and acetic acid (1.1 eq.) in toluene at 75 °C under argon atmosphere for 20 h. It was found that the expected 1-phenyl 2,8-dioxabicyclo [3.3.1] nonane (**3a**) was obtained only in 16% yield (Table 1, entry 1). The structure of **3a** was unambiguously confirmed by its ^{1}H NMR, ^{13}C NMR, HRMS spectra and X-ray crystallographic analysis (see Fig. 2 and the corresponding datablock was in the Supporting Information).[20] A brief survey on the proportion of **1a** and **2a** indicated that appropriately excessive **2a** was favorable to the transformation (entries 1–4). **3a** was obtained in relatively higher yield in dichloroethane (DCE) according to the screen of solvents (entries 5–7). The transformation was also attempted under catalysis of other bases and acids, such as DABCO, pyridine, DBU, Ac_2O, TsOH and CF_3CO_2H, but **3a** wasn't isolated in higher yields (entries 8–13). Also, no increasing yield was obtained after increasing the amount of piperidine to 1.0 eq. (entry 14). Next, by decreasing the dosage of piperidine to 0.3 eq., higher yield of 50% was achieved (entry 15). But the yield decreased obviously after continuing decreasing the dosage of piperidine (entry 16). The amount of acetic acid was also explored, but no better results were given (entries 17 and 18). Finally, to our excitement, the product was obtained in excellent yield under solvent-free condition (entry 19). Additionally, slight decreasing in the reaction temperature was favorable to increase the yield, but continuous decreasing the reaction temperature gave the opposite result (entries 21 and 22). After sifting different bases and acids, the optimal conditions were identified as the use of **1a** (1 mmol), piperidine (0.3 eq.), acetic acid (1.1 eq.) under argon atmosphere and solvent-free conditions at 70 °C for 20 h (entry 21 is shown in Table 1 boldly).

Under the optimal conditions, the generality of the reaction was explored for the synthesis of diverse 1-aryl-substituted 2,8-dioxabicyclo [3.3.1] nonanes. Primarily, 1,3-diketone **2a** was used to react with a variety of 2-hydroxybenzaldehyde derivatives (**1**). In all these reactions, products **3** were produced in moderate to good yields (Table 2). The substrates bearing electron-withdrawing substituent such as -F, -Cl, -Br on C-4 or C-5 position of the phenyl ring could react smoothly with **2a** to deliver the corresponding **3b**, **3c**, **3e**, **3g** in excellent yields (70–85%) (entries 2, 3, 5 and 7). However, the halogen atom on the C-3 position was found to be unfavorable for this transformation due to steric hindrance

Table 1
Optimization studies for the synthesis of 2,8-dioxabicyclo [3.3.1] nonane derivative **3a**.[a]



Entry	1a:2a	Base	Acid	Solvent	T/°C	Yield/%[b]
1	1: 2	Piperidine	AcOH	toluene	75	16
2	1: 2.5	Piperidine	AcOH	toluene	75	17
3	1: 3	Piperidine	AcOH	toluene	75	27
4	1: 3.5	Piperidine	AcOH	toluene	75	23
5	1: 3	Piperidine	AcOH	THF	75	22
6	1: 3	Piperidine	AcOH	CH_3CN	75	28
7	1: 3	Piperidine	AcOH	DCE	75	45
8	1: 3	DABCO	AcOH	DCE	75	36
9	1: 3	Pyridine	AcOH	DCE	75	NR
10	1: 3	DBU	AcOH	DCE	75	trace
11	1: 3	Piperidine	Ac_2O	DCE	75	NR
12	1: 3	Piperidine	TsOH	DCE	75	NR
13	1: 3	Piperidine	CF_3CO_2H	DCE	75	NR
14	1: 3	Piperidine[c]	AcOH	DCE	75	40
15	1: 3	Piperidine[d]	AcOH	DCE	75	50
16	1: 3	Piperidine[e]	AcOH	DCE	75	26
17	1: 3	Piperidine[d]	AcOH[f]	DCE	75	38
18	1: 3	Piperidine[d]	AcOH[g]	DCE	75	41
19	1: 3	Piperidine[d]	AcOH	–	75	78
20	1: 3	Piperidine[d]	AcOH	–	65	57
21	**1: 3**	**Piperidine[d]**	**AcOH**	–	**70**	**89**
22	1: 3	Piperidine[d]	AcOH	–	80	77
23	1: 3	DABCO	AcOH	–	70	39
24	1: 3	Pyridine	AcOH	–	70	NR
25	1: 3	DBU	AcOH	–	70	trace
26	1: 3	Piperidine	Ac_2O	–	70	NR
27	1: 3	Piperidine	TsOH	–	70	NR
28	1: 3	Piperidine	CF_3CO_2H	–	70	NR
29	1: 3	Piperidine		–	70	NR

[a] All reactions were conducted under the following conditions unless otherwise indicated: 1a (1 mmol), base (0.6 eq.) and acid (1.1 eq.) in anhydrous solvent (2 mL) under argon atmosphere for 20 h.
[b] Isolated yield.
[c] 1.0 eq. piperidine was used.
[d] 0.3 eq. piperidine was used.
[e] 0.2 eq. piperidine was used.
[f] 1.0 eq. AcOH was used.
[g] 1.2 eq. AcOH was used.

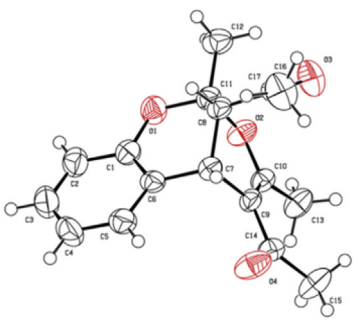


Fig. 2. X-ray crystallography of 3a.

Please cite this article in press as: Yang D-S, et al., A mild and one-step synthesis of 2,8-dioxabicyclo [3.3.1] nonane derivatives via classical Knoevenagel condensation, Tetrahedron (2017), http://dx.doi.org/10.1016/j.tet.2017.07.054