Tetrahedron 70 (2014) 2180–2189

Contents lists available at ScienceDirect

Tetrahedron

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

A novel construction of quino-fused tropone skeleton: first synthesis of 12*H*-benzo[4,5]cyclohepta[1,2-*b*]quinolin-12-one derivatives

Wentao Gao *, Xueda Xing, Yang Li, Shuai Lan

Institute of Superfine Chemicals, Bohai University, Jinzhou 121000, China

ARTICLE INFO

Article history:
Received 29 September 2013
Received in revised form 21 January 2014
Accepted 23 January 2014
Available online 11 February 2014

Keywords:
Quinoline
Tropone
Polyphosphoric acid
Intramolecular Friedel–Crafts acylation
One-pot synthesis

ABSTRACT

In the present investigation, the incorporation of both quinoline moiety and tropone ring in a molecule frame work in fused form leading to a series of structurally novel and biologically intriguing quinoline/tropone hybrids 12*H*-benzo[4,5]cyclohepta[1,2-*b*]quinolin-12-one derivatives has been first achieved through a simple, and economical two-step procedure, involving the one-pot synthesis of (*E*)-2-(arylvinyl)quinoline-3-carboxylic acids followed by intramolecular Friedel–Crafts acylation reaction using polyphosphoric acid (PPA).

1. Introduction

The cyclohepta-2,4,6-trienone, better known under the common name tropone, is a pharmaceutically important structural unit. Compounds bearing this moiety possess a broad spectrum of biological activities.[1–3] Especially, some tropones fused to aromatic or heteroaromatic rings are an important class of compounds, which represent privileged moieties in medicinal chemistry,[4] and are ubiquitous sub-structure associated with biologically active natural products, such as Colchicine (**I**, Fig. 1),[5] Caulersine (**II**, Fig. 1),[6] Tintamine (**III**, Fig. 1),[7] and Pareitropone (**IV**, Fig. 1).[8] Recent studies have suggested that some heterocycles with the combination of a tropone ring could increase their biological activities or create new medicinal properties due to the different electronic distribution and the additional basic character of the tropone ring.[9,10] In addition, the tropone moiety also plays an important role in molecular assemblies for a faster and efficient lead generation towards the new drug discovery.[11–13] Despite featuring only seven ring carbon atoms and no stereocentres, the synthesis of structurally novel ring-fused is still a considerable synthetic challenge as tropone derivatives are scarce in nature,[14] occurring only in lower plants and fungi,[15] and limited information is available on these compounds. On account of these facts, extensive synthetic efforts have been devoted surrounding the tropone ring to design and synthesize novel ring-fused tropone systemes.[16–19]

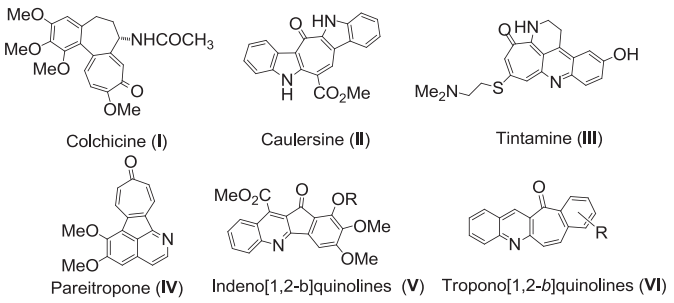


Fig. 1. Examples of hetero-fused tropones (**I**–**VI**).

On the other hand, it has been well-established that planar polycyclic-fused quinoline system, especially tri- or tetracyclic-fused frame work could intercalate into base pairs of DNA as an intercalator to induce topoisomerase II dependent DNA cleavage,[20,21] thereby exhibiting significant biological properties, such as antitumoral, anti-cancer,[22] anti-inflammatory,[23] antituberculosis,[24] and antiplasmodial activities.[25] For example, tetracyclic indenoquinoline derivatives (**V**, Fig. 1) were reported to show potent antiproliferative activities against breast (MCF-7), lung epithelial (A-549), and cervical (HeLa) adenocarcinoma cells.[26] As a consequence, the remarkable bioactivities along with the unique structural arrays displayed by these tetracyclic-fused quinoline systems have made them a particularly appealing target for the synthetic efforts.[27–30]

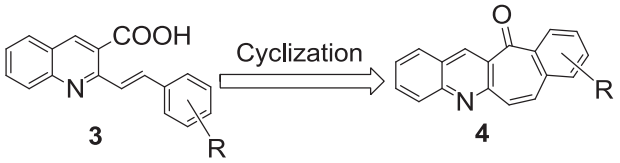
* Corresponding author. Tel./fax: +86 416 3400266; e-mail address: bhuzh@163.com (W. Gao).

0040-4020/$ – see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2014.01.049

Considering the above valid points, and in view of structural diversity playing a prominent role in medicinal and combinatorial chemistry,[31] we conceived that the incorporation of the tropone nucleus into the planar tetracyclic-fused quinoline systems leading to new prototypes, as possible drug-like candidates for pharmacological studies, would be of synthetic importance. Therefore, in the context of our ongoing studies concerning the synthesis of potential biologically active hybrid molecules,[32–38] we wish to report, herein, a facile and inexpensive procedure for the preparation of planar linearly tetracyclic-fused benzotroponoquinoline systems, wherein the tropone ring is fused at its 2,3-position to the b-position of quinoline ring to give a compact structure like the compounds **VI** in Fig. 1. To the best of our knowledge, this type of polycyclic-fused structure is still unprecedented.

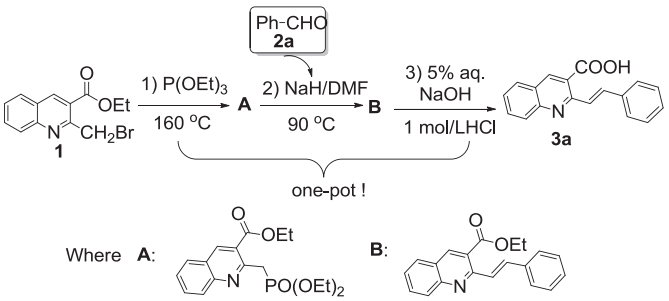
2. Results and discussion

It is well known that the intramolecular Friedel–Crafts acylation reaction of some appropriate aryl- or heteroarylcarboxylic acids has been particularly useful in synthetic organic chemistry,[39–41] since this reaction could result in the construction of an extra ring by generation of a new C–C bond, including seven-membered ring construction.[42,43] For example, Karcher and co-worker reported the intramolecular Friedel–Crafts acylation reaction of 2-styrylnicotinic acid for the synthesis of benzotroponopyridine derivatives.[9] In this regard, we recently reported the intramolecular Friedel–Crafts acylation reaction of 2-aryloxymethylquinoline-3-carboxylic acids for the construction of polycyclic-fused benzo[6,7]oxepino[3,4-*b*]quinolin-13(6*H*)-ones.[32,38] Taking these observations into account, we reasoned that if we could achieve the facile synthesis of suitably 2-styrylquinoline-3-carboxylic acid derivatives (**3**) as the tetracyclic precursors, it might be possible to convert them into the desired tetracyclic quino-fused tropone systems **4** via the intramolecular cyclization strategy as shown in Scheme 1.



Scheme 1. Possible construction of quino-fused tropone systems via Friedel–Crafts cyclization reaction.

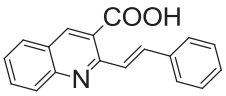
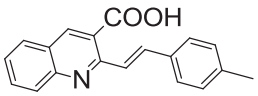
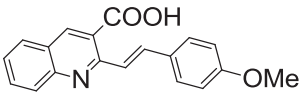
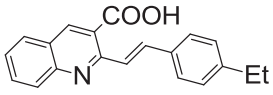
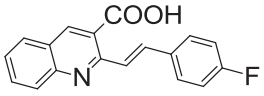
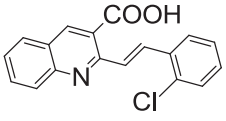
Thus, the key to implement our strategy was the realization of the facile preparation of the key substrates **3**. Prior to the current investigation, a few related examples involving the synthesis of 2-styrylpyridine3-carboxylic acids, structurally analogous to **3**, have been reported.[9,17] Although the two methodologies are elegant and impressive, our attempts to follow both routes to synthesize our 2-styrylquinoline-3-carboxylic acid derivatives were unfruitful, and no promising result was obtained. Therefore, we felt that there was a real need for the development of a direct and concise method to synthesize the required substrates **3**. To this end, we postulated an efficient and attractive one-pot reaction procedure. As outlined in Scheme 2, ethyl 2-(bromomethyl)quinoline-3-carboxylate (**1**) was first subjected to the Arbuzov reaction with triethyl phosphate at 160 °C. After the complete conversion of the starting material to the corresponding intermediate **A** (TLC), triethyl phosphate was evaporated to dryness under reduced pressure. Subsequently, we conducted the Horner–Emmons olefination reaction of **A** with benzaldehyde (**2a**) by adding directly a solution of 1.1 equiv of **2a** in DMF to the residue at 90 °C. We examined this reaction by using different bases (NaOH, K_2CO_3, Et_3N, EtONa, *t*-BuOK, NaH) and varying their equivalents, from one to three, separately. We found that the reaction could not occur upon using NaOH, K_2CO_3 or Et_3N, whereas an incomplete reaction was observed when using EtONa as base. The use of *t*-BuOK gave an intractable complex mixture that we could not separate any desired product in appreciable yield. To our delight, we discovered that 1.1 equiv of NaH were suitable to promote the reaction, which was completed within 2 h as TLC indicated the absence of intermediate **A**. Since the newly-formed olefination product **B** did not interfere with further ester hydrolysis reaction, purification at this stage was unnecessary. Accordingly, we simply added 5% aqueous NaOH solution directly to the reaction mixture and continued to reflux for 2 h. After the reaction was completed followed by an acidic work-up, the corresponding free carboxylic acid **3a** was obtained in a good overall yield of 76%. The stereochemistry of **3a** was established as an *E*-stereoisomer on the basis of its ^{1}H NMR spectrum, which showed the mutual coupling constant value J=15.6 Hz of the two arising vinylic protons CH=CH at 8.08 and 8.17 ppm, respectively.



Scheme 2. One-pot synthesis of 2-styrylquinoline-3-carboxylic acid (**3a**).

Thereafter, various aromatic aldehydes **2b–r** with differing electronic properties were subjected to the one-pot sequence under the same reaction conditions for the synthesis of a series of 2-styrylquinoline-3-carboxylic acid derivatives (**3b–r**). The reaction results were listed in Table 1.

Table 1
Synthesis of differently substituted (*E*)-2-(arylvinyl) quinoline-3-carboxylic acids (**3a–r**)

Entry	Product	3a–r	Yield[a] (%)
1		**3a**	76
2		**3b**	75
3		**3c**	83
4		**3d**	71
5		**3e**	74
6		**3f**	80

(*continued on next page*)