Tetrahedron Letters 59 (2018) 163–166

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Total synthesis of tetracyclic kynurenic acid analogues isolated from chestnut honey

Raffaella Cincinelli [a,*], Giangiacomo Beretta [b], Sabrina Dallavalle [a]

[a] Department of Food, Environmental and Nutritional Sciences, Division of Chemistry and Molecular Biology, Università degli Studi di Milano, via Celoria 2, I-20133 Milano, Italy
[b] Department of Environmental Science and Policy ESP, Università degli Studi di Milano, Via Mangiagalli 25, 20133 Milano, Italy

ARTICLE INFO

Article history:
Received 3 November 2017
Revised 29 November 2017
Accepted 3 December 2017
Available online 6 December 2017

Keywords:
Kynurenic acid analogues
Chestnut honey
Natural products
Microwave assisted synthesis

ABSTRACT

A short and efficient synthesis of novel tetracyclic Kynurenic acid analogues, isolated from chestnut honey, is described. The crucial step of the strategy was a MW-assisted cyclization of enamines of ethyl dioxohexahydropyrrolizine and 2,3-dioxooctahydroindolizine carboxylates to obtain 2,3,6,11b-tetrahydro-1H-pyrrolizino[2,1-*b*]quinoline-5,11-dione and 5,8,91,011,11a-hexahydroindolizino[2,1-*b*]quinoline-6,12-dione, respectively. Because of its modular nature, the synthetic strategy can have value as a general method for the preparation of compounds containing these new heterocyclic scaffolds.

Kynurenic acid (KYNA), an endogenous, non-selective antagonist of ionotropic glutamate receptors, is commonly considered as a final metabolite of tryptophan via the kynurenine pathway (KP).

Recent studies provided evidence for an important role of kynurenine pathway metabolites in several neurological, psychiatric and neurodegenerative diseases, with particular emphasis on the putative neuroprotective activity exerted by KYNA.[1] The biological activity of KYNA is due to its antagonizing capacity toward the glycine site of the NMDA (*N*-methyl-D-aspartate) receptors and/or the cholinergic α7 nicotine receptors. However, concomitant or alternative involvement of other pharmacological targets responsible for its electrophysiological and behavioral actions cannot be excluded.[2]

KYNA is present in several food products, with the highest known concentrations found in chestnut honey.[3] 6-Hydroxy-KYNA and KYNA are also present in the plant kingdom with a taxa-specific distribution of the former.[4] The observation of significant levels of KYNA in different medicinal plants suggested that it may contribute to their therapeutic potential, especially in the digestive system.[5]

Interestingly, recent studies consistently demonstrated that chestnut honey also contains tetracyclic KYNA derivatives, with a tetrahydropyrrolizinoquinolinedione (compound **1**, Fig. 1) or a hexahydroindolizinoquinolinedione (compound **2**, Fig. 1) core.[6] These substances originate mainly from the nectar of male flowers of chestnut.[7] Their biosynthesis is also intriguing, as they probably derive from KYNA,[7] differently from the isomeric fungal metabolite tetrahydroquinolactacide,[8] whose biosynthesis most likely starts from anthranilic acid.[9]

Currently, the biological function(s) and therapeutic potentiality of derivatives **1** and **2** are unknown.

Hence, the aim of the present study was to set up a synthetic procedure for these new quinolinone alkaloids which may – in principle – have value in the preparation of the natural compounds themselves as well as in synthesizing analogues for structure-activity relationship studies.

Initially, we focused on the synthesis of compound **1**. We envisioned that the most straightforward approach could be based on the construction of the tetracyclic system starting from kynurenic acid.

Thus, disconnection at the amide bond level of the compound **1** gave as precursor the key intermediate **A**, which should be accessible by metal-catalyzed cross-coupling reaction between a functionalized kynurenic acid **B** and a boronic acid **C** (Scheme 1, path I).

The *N*-benzyl protected coupling partner **B** (compound **5**) was easily obtained by treatment of *N*-benzylaniline **3** with DMAD (dimethyl acetylenedicarboxylate) in methanol at reflux, followed by cyclization with Eaton's reagent[10] to give *N*-benzyl kynurenic acid methyl ester (**4**). Iodination[11] provided intermediate **5** in good yield.

The *N*-Boc protected partner **C** (compound **6**) was obtained from commercially available *N*-Boc pyrrole-2-boronic acid by

* Corresponding author.
E-mail address: raffaella.cincinelli@unimi.it (R. Cincinelli).

https://doi.org/10.1016/j.tetlet.2017.12.015
0040-4039/

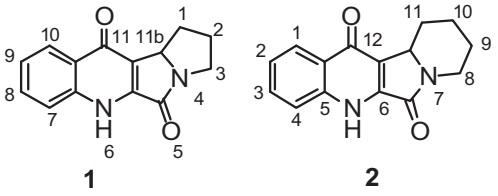
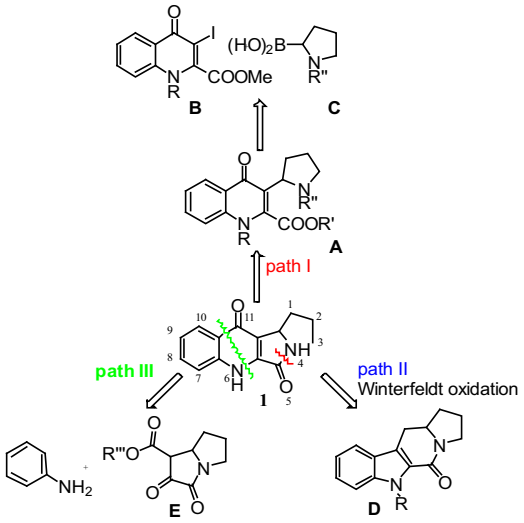


Fig. 1. Structures of compounds **1** and **2** isolated from chestnut honey.



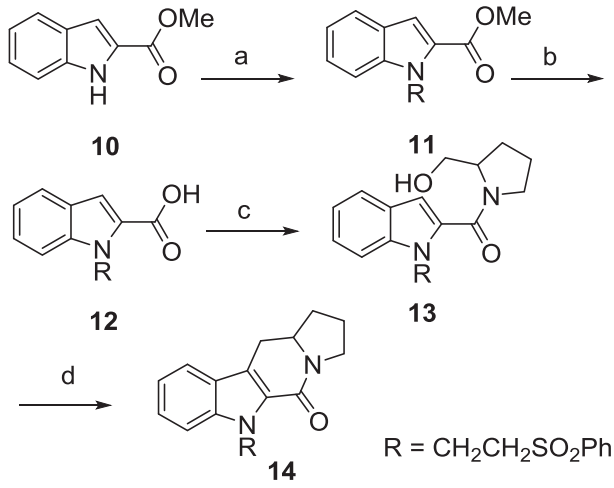
Scheme 1. Retrosynthetic analyses of compound **1**.

hydrogenation with PtO_2 in ethyl acetate at room temperature (Scheme 2). Once prepared the two fragments, we had to couple them to obtain compound **7**.

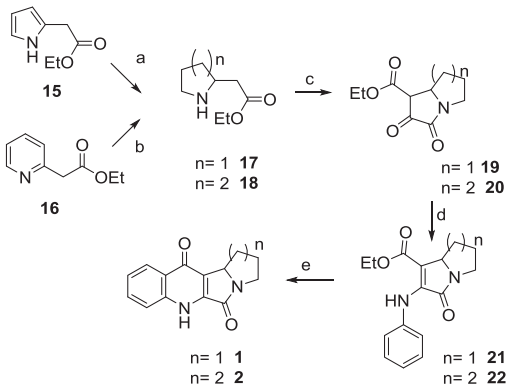
Initial efforts to effect the carbon-carbon coupling reaction, carried out using $Pd(PPh_3)_4$ and aqueous Na_2CO_3 in toluene at 80 °C, were unsuccessful. Various attempts of coupling made with different bases (K_2CO_3, K_3PO_4, $CsCO_3$) different phosphine ligands (Pd(dppf), $Pd(dba)_2$) and a variety of solvents (dioxane, THF and DME) always gave complex reaction mixtures.

Stille cross coupling reaction was also unsuccessful. Stannane **8** was prepared from *N*-Boc pyrrolidine and n-Bu_3SnCl with *sec*BuLi in THF. Reaction of this latter with **5** in the presence of $Pd(PPh_3)_4$ in dioxane[12] did not provide the expected product (Scheme 2).

A possible explanation of these failures in coupling reactions is the poor reactivity of alkyl boronic acids. Aryl-alkyl Suzuki-Miyaura cross-couplings are often complicated by reduction and



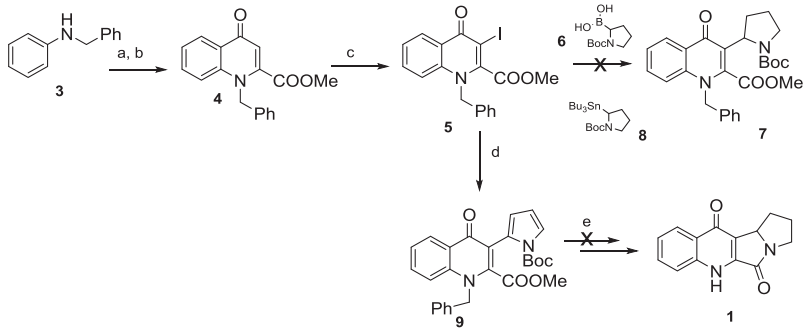
Scheme 3. Synthesis of compound **14**. Reagents and conditions: a) $ClCH_2CH_2SO_2Ph$, NaH, DMF, N_2, rt, 61%; b) $LiOH.H_2O$, THF/H_2O 1:1, 98%; c) EDCI (1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride), HOBt (hydroxybenzotriazole), prolinol, THF, N_2, rt, 86%; d) TFA, 1,2-dichloromethane, 50 °C, N_2, 12%.



Scheme 4. Synthesis of compounds **1** and **2**. Reagents and conditions: a) Rh/Al_2O_3 5%, CH_3COOH, H_2, 1 atm, 79% b) PtO_2, EtOH, HCl 6 M, H_2 1 atm; 74% c) diethyl oxalate, EtONa, EtOH, reflux, N_2, 80% for **19** and 70% for **20**; d) aniline, toluene, reflux, 70% for **21** and 53% for **22**; e) DMF, 245 °C, MW, 45% for **1** and 60% for **2**.

isomerization side reactions as a result of the presence of β-hydrogen atoms in the alkyl group.[13]

The use of *N*-Boc-2-pyrroleboronic acid instead of the corresponding alkyl boronic acid **6** easily afforded the coupling product **9**,[14] but the successive reduction of the ring together with the removal of the protecting benzyl group failed, even by hydrogenation at high pressure[15] (Scheme 2).



Scheme 2. Synthesis of compound **9**. Reagents and conditions: a) DMAD, MeOH, reflux, 85%; b) $P_2O_5/MeSO_3H$, N_2, 50 °C, 82%; c) I_2, CAN, N_2, 50–80 °C, 98%; d) $Pd(PPh_3)_4$, $NaHCO_3$, DME, 2-pyrrol boronic acid, N_2, reflux, 64%; e) H_2 40 atm, Pd/C 10%, MeOH, rt.