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ORIGINAL ARTICLE

A new approach to 3-substituted tetrahydro-β-carboline derivative via diethyl acetamidomalonate

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Abstract Strategically a new approach for the synthesis tetrahydro-β-carboline unit with the aid of diethyl acetamidomalonate as a glycine equivalent has been described.

Keywords Diethyl acetamidomalonate · Indole alkaloids · Tetrahydro-β-carboline · Unusual α-amino acid derivatives

Introduction

Tetrahydro-β-carboline (THBC) unit is an important structural element present in many biologically active alkaloids (Bailey and Hollinshead 1988; Soderberg and Dantale 2003; Szawkało et al. 2007). A number of THBC derivatives exhibit promising biological activity. To this end, various β-carboline derivatives are involved in the treatment of alcoholism (Cook et al. 2010). In addition, indole alkaloids (Jenkins et al. 2008; Shen et al. 2005; Moody et al. 1995; Moody and Roffey 2000) (Fig. 1) displayed interesting physiological properties and also show diverse medicinal applications. For example, reserpine exhibits cardiovascular effect (Chopra et al. 1933; Petter and Engelmann 1974).

Generally, syntheses of various β-carboline-based indole alkaloids involve utilization of traditional reactions such as the Bischler–Napieralski (Ho and Lin 2008; Liu and Xu 1989; Magnus et al. 1999) and the Pictet–Spengler reaction (Cook and Cox 1995; Mergott et al. 2008; Ma et al. 2007) etc. for assembling THBC unit. More recently, intense efforts are directed towards to synthesize THBC skeleton using different approaches (Fujii et al. 2009; Pfeffer et al. 2010; Shipman et al. 2008). As a part of major project aimed at developing new methodologies for the synthesis of unusual α-amino acid (AAA) derivatives (Kotha et al. 2010) we have utilize diethyl acetamidomalonate (DEAM) as a useful glycine equivalent (Kotha and Singh 2004; Kotha and Halder 2010). In this regard, we envisioned that DEAM is an attractive option for the synthesis of THBC derivatives (Fig. 2).

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Experimental

General procedure for tetrahydro-β-carboline derivative

To a stirred suspension of potassium carbonate (5 equiv.) and DEAM (1 equiv.) in dry acetonitrile was added *N*-protected indole dibromide **10** after 15 min. The resulting reaction mixture was stirred at 70°C for 8 h under nitrogen. At the conclusion of the reaction (TLC monitoring), the reaction mixture was cooled and filtered on a Celite pad. The filtrate was evaporated at reduced pressure. The residue was purified by silica gel column chromatography (30% petroleum ether/ethyl acetate) to give the desired compound as white solid.

*Spectroscopic data for compound: (**11**)*

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (t, $J = 7.17$ Hz, 6H), 2.31 (s, 3H), 3.51 (s, 2H), 4.07 (s, 3H), 4.16–4.21 (m, 4H), 5.05 (s, 2H), 7.26–7.33 (m, 2H) 7.46 (d, $J = 6.72$ Hz, 1H), 8.05(d, $J = 7.94$ Hz, 1H). ^{13}C NMR (100.5 MHz $CDCl_3$): δ 14.0, 22.9, 27.9, 45.9, 54.1, 62.4, 67.6, 113.8, 115.7, 118.4, 123.6, 125.0, 128.4, 167.5, 173.0. HRMS (Q-ToF):

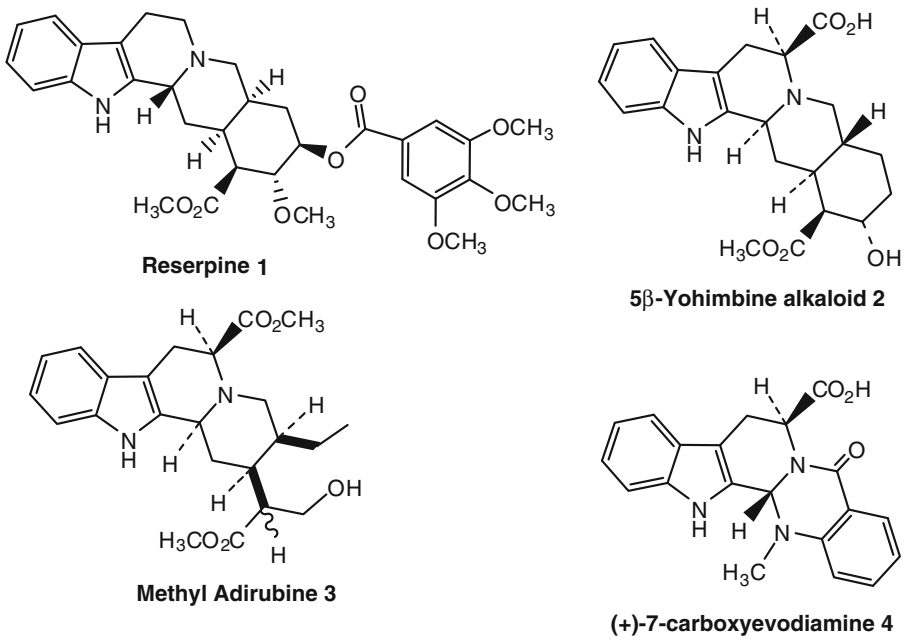

Fig. 1 Various alkaloids containing tetrahydro-β-carboline as a core unit

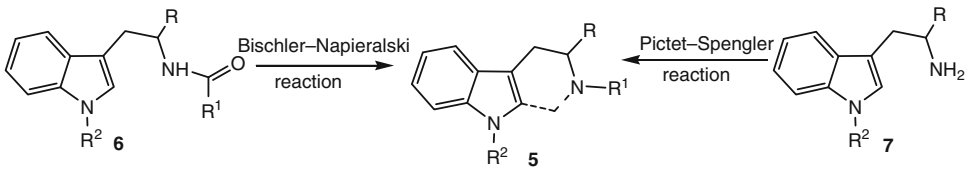

Fig. 2 Synthetic approach THBC derivative by Bischler–Napieralski and Pictet–Spengler reaction

m/z calcd for $C_{21}H_{24}N_2O_7$ (M+H) calcd 417.1662 obs 417.1655. M.P. 174–178°C.

*Spectroscopic data for compound: (**12**)*

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (t, $J = 7.17$ Hz, 6H), 2.22 (s, 3H), 3.57 (s, 2H), 4.21–4.25 (m, 4H), 4.97 (s, 2H), 6.75 (d, $J = 8.2$ Hz, 1H), 7.05 (t, $J = 7.33$ Hz, 1H), 7.21 (t, $J = 7.63$ Hz, 3H), 7.47–7.55 (m, 2H), 7.66–7.55 (m, 2H). ^{13}C NMR (100.5 MHz $CDCl_3$): δ 13.8, 22.6, 27.8, 45.4, 62.3, 67.5, 114.3, 114.9, 118.4, 123.3, 124.0, 128.5, 128.9, 129.0, 130.6, 132.8, 134.7, 136.4, 167.4, 168.8, 172.9. HRMS (Q-ToF): *m/z* calcd for $C_{26}H_{26}N_2O_6$ (M+H) calcd 463.1869 obs 463.1859. M.P. 134–138°C

*Crystal structure determination for **11***

Suitable X-ray quality crystals of **11** could be grown from acetonitrile/*n*-hexane solvent mixture at RT, and X-ray diffraction studies were undertaken. The details of the crystal data have been deposited with the Cambridge Crystallographic Data Center as Supplementary Publication No. CCDC-776486. X-ray crystallographic data were collected from single-crystal samples of **11** (0.23 × 0.18 × 0.13 mm^3) mounted on a Oxford Diffraction XCALIBUR-S CCD system equipped with graphite-monochromated Mo Kα radiation (0.71073 Å). The data were collected by the ω–2θ scan mode, and absorption correction was applied by using Multi-Scan. The structure was solved by direct methods (SHELXS-97) and refined by full-matrix least squares against F^2 using SHELXL-97 software.

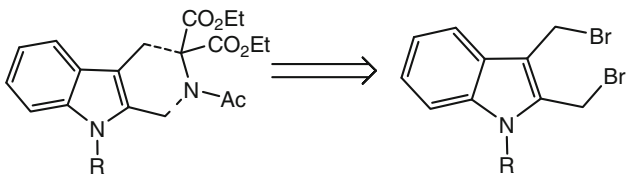

Fig. 3 Retrosynthetic analysis towards the THBC derivative

Result and discussion

In view of our experience to design unusual AAA derivatives via building block approach (Kotha 2003) we conceived DEAM as a useful starting material for construction of THBC unit which was not reported previously. In other words, THBC derivatives can be assembled from indole derivatives instead of tryptophan derivatives (Fig. 3).

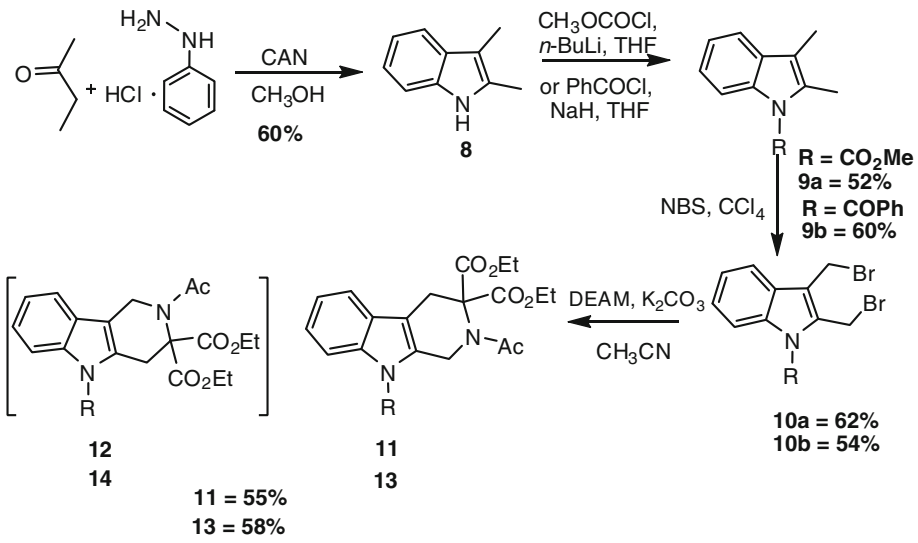

Fig. 4 Synthesis of THBC derivatives

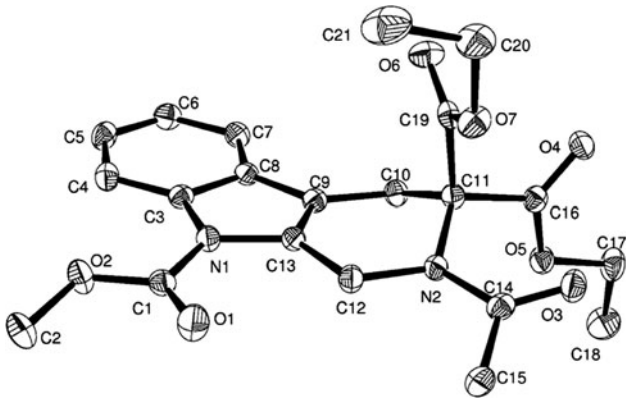

Fig. 5 ORTEP diagram of compound **11**

To begin with, 2,3-dimethyl indole **8** was prepared via Fischer indole cyclization using phenylhydrazine hydrochloride with methyl ethyl ketone in presence of ceric ammonium nitrate (CAN) (Fig. 4). Later 2,3-dimethyl indole **8** was converted to the corresponding *N*-protected 2,3-dimethyl indole derivatives using benzoyl chloride or methyl chloroformate (Verma et al. 2009). The required dibromo indole derivative **10** was prepared by following literature procedure (Srinivasan and Saroja 1984) starting with the *N*-protected 2,3-dimethyl indole **9** using *N*-bromosuccinimide (NBS) under free radical conditions. Next, the dibromide **10** (1 equiv.) in dry acetonitrile was treated with DEAM (1 equiv.) and powdered potassium carbonate (6 equiv.) to generate single coupling compound. The gross structure of the coupling product was based on the spectral data, such as ^{1}H and ^{13}C NMR and HRMS. In this regard one can think of two possible regioisomer **11** or **12.** The unambiguous structural assignment for the DEAM coupling product **11** has been achieved with the aid of single crystal X-ray diffraction technique. The molecular structure of **11** and structure refinement parameters are included in Fig. 5. The mechanism for the formation of single regioisomer is not clear at this point. However, we plan to explore this aspect in a detail manner.

Since THBC unit is a core structural element for assembling various alkaloids, our methodology opens up a new retrosynthetic path to various β-carboline-based natural products and drugs.

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