Molbank **2013**, M811; doi:10.3390/M811

OPEN ACCESS

molbank

ISSN 1422-8599

www.mdpi.com/journal/molbank

Short Note

Ethyl 2-(3-Methyl-5-oxo-4,5-dihydro-3*H*-benzo[*e*][1,4]diazepin-2-ylamino)benzoate

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Received: 25 October 2013 / Accepted: 9 December 2013 / Published: 12 December 2013

Abstract: A simple route for synthesis of ethyl 2-(3-methyl-5-oxo-4,5-dihydro-3*H*-benzo[*e*][1,4]diazepin-2-ylamino)benzoate is developed. The present work involves condensation of 2-(2-nitrobenzamido)propanoic acid with ethyl anthranillate followed by the H_2/Pd/C reduction to give the amino ester which upon heating in DMF in the presence of $FeCl_3$ affords the title compound. The structure of the title compound was established on the basis of ^{1}H-NMR, ^{13}C-NMR and mass spectral data.

Keywords: benzo[*e*][1,4]diazepine; ferric chloride; cyclization

Introduction

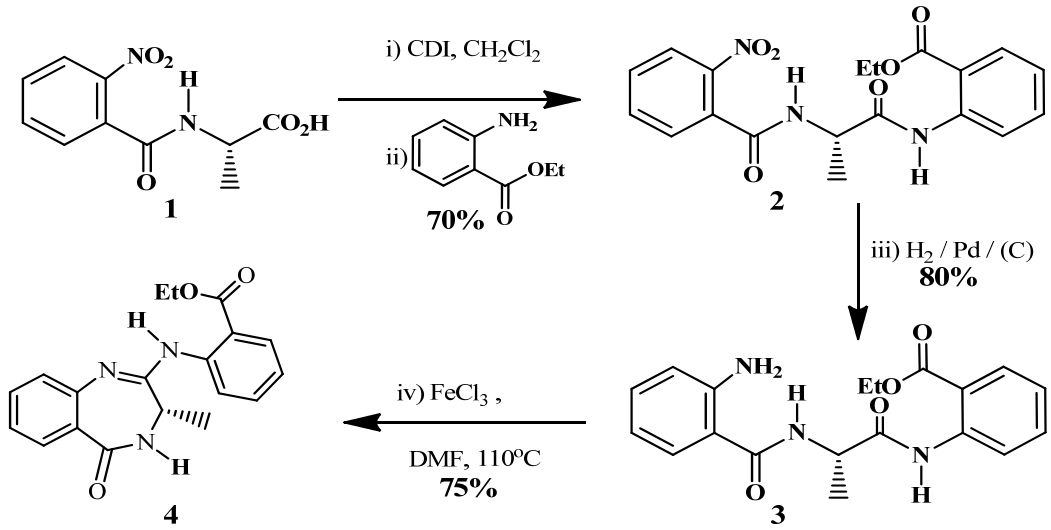
The growing importance of substituted [1,4]benzodiazepines in the field of medicinal chemistry as potential chemotherapeutic agents have incited the organic synthetic community to devise efficient methodologies to construct these bicyclic hetero-compounds [1–5].

Little attention has been devoted to the structural perturbations caused by substitution at C-2 position in 1,4-diazepines possessing an imine bond (N1-C2) [6]. This fact, coupled with continuation of our work on the cyclization modes of tripeptide containing two units of anthranilic acid and an amino acid, prompted us to devise an efficient method of synthesis for benzo[*e*][1,4]diazepinone using transition metals [7–9]. The synthetic procedure described here can be protracted to prepare a wide range of derivatives for further biological evaluation.

Results and Discussion

(*S*)-2-(2-Nitrobenzamido)propanoic acid **1** [10] was coupled with ethyl 2-aminobenzoate using a standard procedure to afford **2** in good yield (70%, Scheme 1). The reduction of the nitro group was conducted under mild conditions (H_2/Pd/(C)) to furnish the corresponding amine **3**. The ^{1}H-NMR spectrum of **3** indicated the presence of NH_2 group by displaying a broad D_2O exchangeable signal at δ 5.45. Furthermore, the methine proton was observed as doublet of quartet at δ 4.73, the ethyl group protons were observed as triplet and quartet at δ 1.31, 4.29, respectively.

Scheme 1. Synthesis of (*S*)-ethyl 2-(3-methyl-5-oxo-4,5-dihydro-3*H*-benzo[*e*][1,4]diazepin-2-ylamino)benzoate (**4**).



The synthesis of the title compound **4** was accomplished by heating amine **3** in DMF at 110 °C in the presence of fused transition metal chlorides. Three transition metal chlorides ($MgCl_2$, $ZnCl_2$ and $FeCl_3$) were implemented. The cyclization of amine **3** was best achieved using fused $FeCl_3$ to afford the title benzodiazepinone compound in 75% yield.

The ^{1}H-NMR spectrum of the title compound displayed the methine proton attached to the stereogenic center at δ 4.23 as quartet. Moreover, and a doublet signal representing the methyl group next to stereogenic carbon was observed at 1.82 ppm. The ^{13}C-NMR spectrum displayed a signal at 21.9 ppm for the methyl carbon next to the stereogenic center. The mass spectrum of **4** showed the M^+ peak at *m/z* 337.9 attributed to the molecular formula $C_{19}N_3O_3H_{19}$ ($M+H^+$).

Experimental

Amine **3** (400 mg, 1.13 mmol) was dissolved in DMF (30 mL) containing fused $FeCl_3$ (543.08 mg, 3.39 mmol). The resulting mixture was then heated with continuous stirring in oil bath for 24 h at 110 °C. The reaction mixture was cooled to room temperature, diluted with water (100 mL) and then extraction with 40% EtoAc/hexane (2 × 100 mL). The combined organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel eluting with 40% ethyl acetate in hexane to give the title compound **4** (285 mg, 75% yield) as a pale yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.28 (t, *J* = 7.1 Hz, 3H), 1.82 (d, *J* = 7.2 Hz, 3H) 4.23 (q, *J* = 7.0 Hz, 1H) 5.65

(q, *J* = 7.2 Hz, 2H) 7.05 (t, *J* = 4 Hz, 1H), 7.45 (m, 2H), 7.70 (m, 2H), 7.95 d, *J* = 5 Hz, 1H), 8.19 (s, 1H), 8.45 (m, 2H), 8.60 (d, *J* = 3 Hz, 1H), 11.5 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 19.0, 21.9, 34.8, 58.7, 120.7, 125.3, 128.0, 131.9, 132.1, 132.4, 135.7, 139.3, 139.4, 145.6, 149.0, 152.6, 165.7, 173.0; ESI-MS *m/z* 337.9 (M^+); Anal Calcd. for $C_{19}H_{19}N_3O_3$: C, 67.64; H, 5.68; N, 12.46; O, 14.23. Found: C, 67.69; H, 5.63; N, 12.52.

Acknowledgments

This work was supported by the Deanship of Research at Jordan University of Science and Technology.

Conflicts of Interest

The authors declare no conflict of interest.

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