Scientific Paper

Synthesis of *N*-Substituted Quinazolino[1,4]-benzodiazepine: A Facial Route to *N*-Benzylsclerotigenin

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Received 07-04-2005

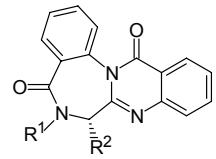
Abstract

Synthesis of *N*-benzylsclerotigenin was achieved in four steps. Initially, isatoic anhydride was allowed to react with benzylamine and chloroacetyl chloride, respectively. The generated dipeptide derivative was then cylized to [1,4]benzodiazepinedione. Acylation with *o*-nitrobenzoyl chloride furnished a labile [1,4]benzodiazepinedione derivative, which upon reduction afforded *N*-benzylsclerotigenin in high yield. This methodology can be adopted in combinatorial synthesis of *N*-substituted quinazolino[1,4]benzodiazepindione library for biological evaluation.

Key words: quinazolino[1,4]benzodiazepine, anthranilic ring system, *N*-benzylsclerotigenin, naturally occurring ring system

Introduction

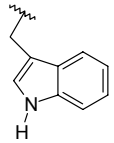
Broad-spectrum man-made insecticides and fungicides have been found to exhibit serious negative impacts on the fragile ecosystem. It is well established that, in their mode of action, these chemicals do not differentiate between useful and harmful organisms. Furthermore, insect and fungus usually develop resistance to such chemicals making them less effective for continuous use.[1] However, recent developments in insecticide and fungicide chemistry have focused on the use of environmentally safe bioactive chemicals to which insects and fungus cannot develop resistence.[2,3,4] The best source for such novel bioactive chemicals is based on chemical ecology where living organisms produce and/or sequester secondary metabolites that serve as chemical defense systems.[2,3,4] Among these potential crop-protecting agents, antiinsectants have recently attracted research interest.[2] Chemical and biological investigations of different fungal species afforded large number of secondary metabolites that possess novel and diverse biological effects including sclerotigenin (**1**),[5] benzolmalvine A (**2**),[6] circumdatin F (**3**),[7,8,9] asperlicin A (**4**)[10,11] and their derivatives. These alkaloids consist of two anthranilic acid units and an amino acid forming together a novel quinazolino[1,4] benzodiazepine ring systems. Sclerotigenin (**1**), isolated in 1999 from Penicllium sclerotigenum Yamamoto, was shown to display potent antiinsectant activity in dietary assays against the crop pest *Helicoverpa* zea.[5] However, it was prepared in 1977 before its identification as a natural product.[12] The total synthesis of Sclerotigenin was recently reported by Thomas,[13] Bergman[14] and Snider.[15] These reports employed in a key step either ammonia gas at 60 °C which is difficult to handle or 2-azidobenzoyl chloride which requires several step to prepare and demand the use of phosphine derivatives to promote an intramolecular aza-Witting reaction.



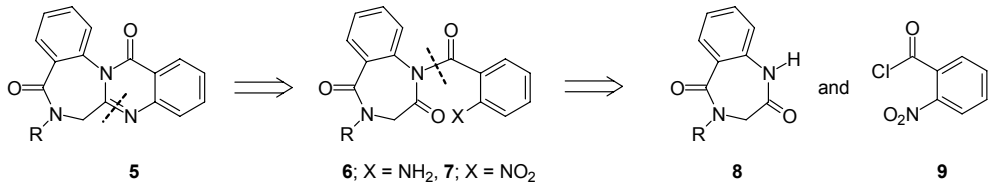
Sclerotigenin (**1**); $R^1 = R^2 = H$

Benzomalvin A (**2**); $R^1 = H$; $R^2 = CH_2Ph$

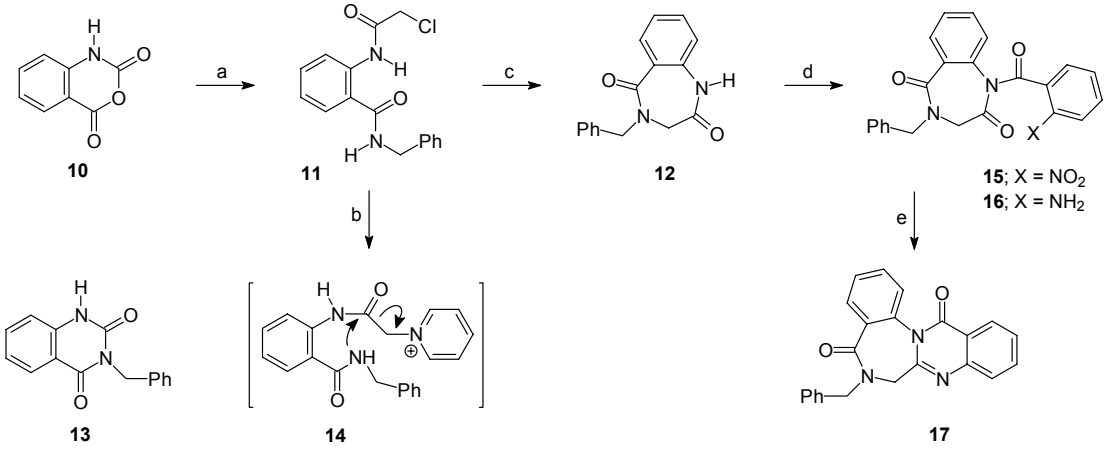
Circumdatin F (**3**); $R^1 = H$; $R^2 = CH_3$

Asperlicin C (**4**); $R^1 = H$; $R^2 =$ 

In our continuing effort to develop a simple synthetic methods to biological active compounds,[16,17,18] we wish to report herein a short and efficient route for the synthesis of the naturally occurring quinazolino[1,4] benzodiazepine system *via* a single reductive-cyclization process using inexpensive 2-nitrobenzoyl chloride.



Scheme 1. Retrosynthesis of quinazolino[1,4]benzodiazepine.



Scheme 2. Synthesis of *N*-benzylsclerotigenin: a: $PhCH_2NH_2$, CH_3CN, reflux, 2 h, then $ClCH_2COCl$, Et_3N, rt, (78%); b: pyridine, reflux, (30%); c: NaH, THF, (94%); d; 2-O_2N-PhCOCl, (49%); e: H_2/ Pd/(C) (77%).

Results and discussion

Our route to synthesis of *N*-substituted quinazo lino[1,4]benzodiazepine ring system **5**, summarized in Scheme 1, involves the novel retrosynthetic approach. This approach is based on cyclization of the intermediate **6**, which could be synthesized after reduction of the nitro group in compound **7**. Compound **7** consists of two parts connected by a carbonyl group. Therefore, benzodiazepinedione **8** and 2-nitrobenzoyl choride (**9**) were predicted to be suitable building blocks for this type of naturally occurring quinazolino[1,4]benzodiaz epine ring system.

In connection with this retrosynthetic analysis, we have investigated the implementation of isatoic anhydide (**10**) as starting material and the benzyl moiety as a protecting group to test our methodology. Thus, the dipeptide **11**[19] was conveniently prepared by one-pot reaction in good yield (78%) by condensation of **10** with benzylamine in dry acetonitrile followed by acylation with chloroacetyl chloride as shown in Scheme 2.

During the step of conversion of dipeptide **11** to benzodiazepinedione **12**[20] by intramolecular S_N2 reaction, it was found that upon heating **11** in pyridine under reflux compound **13** was unexpectedly isolated in 30% yield instead of the anticipated cyclization product **12**. The structure of compound **13** was established on the basis of ^1H and ^{13}C NMR spectroscopy.[21,22,23] The formation of **13** is believed to occur *via* substitution of chloride by pyridine to form the non-isolable intermediate **14**, which undergoes intramolecular nucleophilic attack by the nitrogen atom of the benzyl group as shown in Scheme 2. Fortunately, treatment of dipeptide **11** with the non-nucleophilic base, NaH, in THF at room temperature gave the desired benzodiazepinedione **12** in 94% yield. The ^1H NMR data for compound **12** exhibited two singlets at 4.9 and 3.8 ppm, which are characteristics for the benzylic and seven-membered ring methylene protons, respectively.

With our subgoal attained, we advanced toward the synthesis of intermediate **15**. This was achieved in moderate yield by benzoylation of **12** with 2-nitrobenzoyl chloride (**9**) in the presence of DMAP and Et_3N in dry CH_2Cl_2. The TLC of the reaction mixture indicated the conversion of **12** to the nitro derivative **15** was complete and clean. However, after aqueous work up we observed that the nitro derivative **15** is easily hydrolyzed to the starting materials. Nevertheless, when the reaction mixture was extracted with cold water and purified by silica gel column directly after drying and concentration, the recovered starting material was minimal. The methylene protons of the seven-membered ring in **15** were observed at δ 4.12 (d, 15.7 Hz) and 3.62

(d, 15.7 Hz), indicating that they are non-equivalent on the NMR time scale due to the significant barrier to flipping of the ring.

The planned protocol requires reduction of the nitro group in compound **7** to the corresponding amine. Since the nitro derivative **15** dissociates to the starting materials, a very mild reducing agent (Pd/(C) under a balloon filled with hydrogen gas) was applied. When the reaction was stopped before completion TLC showed the presence of both **15** and *N*-benzylsclerotigenin **17**, whereas the proposed amine intermediate **16** was not observed. After work up, this reaction furnished the required product **17** in good yield (77%). The structure of the final product *N*-benzylsclerotigenin **17** was assigned based on the ^{1}H and ^{13}C NMR spectral data and also by elemental analysis. The benzylic methylene protons of the target compound **17** exhibited two different signals at δ 5.37 (d, 14.8 Hz) and 4.35 (d, 14.8 Hz. The methylene protons of the seven-membered-ring were observed at δ 4.32 (d, 15.1 Hz) and 4.13 (d, 15.1 Hz). In this context, it is important to mention that all attempts to convert *N*-benzylsclerotigenin to the natural sclerotigenin **1** by cleavage of the benzyl group using H_2/Pd(C) were unsuccessful. However, the facile formation of **17** directly from **15** prompted us to investigate the synthesis of quinazolino[1,4]benzodiazep indione alkaloids employing other *N*-protecting groups. The implementation of this methodology presently is under investigation.

Conclusions

We have developed a short, simple and highly reliable route to the synthesis of *N*-substituted quinaz olino[1,4]benzodiazepin-5,13-dione ring system using cheap starting materials. This strategy was successfully applied to the preparation of *N*-benzylscleroteginin. This procedure can also be applied to prepare a wide range of *N*-substituted sclerotigenin derivatives for biological evaluation. In fact, one can adopt this methodology for the combinatorial synthesis of quinazolino[1,4]benzodi azepine libraries for biological evaluation.

Experimental

Melting points (mp) were determined on electrothermal digital melting point apparatus and are uncorrected. Infrared (FT IR) spectra were recorded using a Nicolet-Impact 410 FT IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker, advance DPX-300. The spectral data are reported in ppm (δ) relative to TMS reference line. Mass spectra were recorded on a sector field double focusing unit VG 7070E G.C. mass spectrometer. All the reactions were monitored by thin layer chromatography (TLC).

_N_-Benzyl-2-(2-chloroacetylamino)benzamide (11).

Benzylamine (0.214 g, 2.0 mmol) was added to a solution of isatoic anhydride (**10**) (0.326 g, 2.0 mmol) in acetonitrile (10 mL). The obtained solution was heated under reflux for 3h and then cooled to 0°C. The reaction mixture was treated with triehylamine (0.404g, 4.0mmol) followed by addition of chloroacetyl chloride (0.294 g, 2.6 mmol) in acetonitrile (5 mL). The resulting mixture was stirred at room temperature for 24 h and then concentrated. The residue was dissolved in ethyl acetate. The solution was washed with 5% HCl, water and brine. The separated organic layer was dried ($MgSO_4$) and concentrated giving a dark red residue. The residue was purified on a silica gel column (35% ethyl acetate in hexane) to give **11** (0.472 g). Yield: 78%, mp 153–155 °C. FT IR: (KBr) 3296 (ν_{NH}), 1679 and 1627 ($\nu_{C=O}$), 1597, 1597, 1522 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 11.9.(br, 1H), 8.7 (d, 8.5 Hz, 1H), 7.5–7.3 (m, 7H), 7.1 (t, 8.3 Hz, 1H), 6.6 (br, 1H), 4.7 (bs, 2H), 4.2 (s, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 165.3, 138.6, 137.5, 132.7, 128.9, 128.0, 127.9, 126.5, 123.7, 121.6, 121.2, 44.2, 43.3. MS (EI) m/z (relative intensity %): 302.3 (M^+ ($C_{16}H_{15}O_2N_2Cl$), 1), 196.2 (4), 161.3 (6), 146.2 (9), 132 (14), 120.2 (100).

4-Benzyl-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione (12).

Sodium hydride (NaH, 60%, 0.384 g, 9.6 mmol) was added portion-wise to a solution of chloride derivative **11** (1.210 g, 4 mmol) in dry THF (20 mL). The resulting mixture was stirred at room temperature overnight and then concentrated. The residue was dissolved in ethyl acetate. The resulting solution was washed with 5% HCl and brine. The separated organic layer was dried ($MgSO_4$) and concentrated. The residue was purified on a short column of silica gel (0–30% ethyl acetate in $CHCl_3$) to furnish **12** (1.004 g). Yield: 94%, mp 173–174 °C. FT IR (KBr): 3246 (ν_{NH}), 1696 and 1628 ($\nu_{C=O}$), 1603, 1483 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.5 (br, 1H), 8.2–6.8 (m, 9H), 4.9 (s, 2H), 3.8 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 167.3, 136.2, 135.9, 132.6, 132.0, 128.8, 128.3, 127.9, 126.4, 125.3, 120.7, 52.0, 52.0. Anal. Calcd. for $C_{16}H_{14}O_2N_2$: C 72.17, H 5.29, N 10.52. Found: C 71.95, H 5.28, N 10.55.

3-Benzyl-1*H*-quinazoline-2,4-dione (13).

A solution of chloride derivative **11** (0.908 g, 3 mmol) in pyridine (15 mL) was heated under reflux for 20 min then concentration under reduced pressure. The residue was chromatographed on a silica column (30–40% ethyl acetate in hexane) to give **13** (0.227 g). Yield: 30%, mp 220–222 °C. FT IR (KB): 3438 (ν_{NH}),

1713 ($\nu_{C=O}$), 1653 ($\nu_{C=O}$), 1452 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.16 (br s, 1H), 8.14 (d, 7.7 Hz, 1H), 7.6 (m, 1H), 7.53 (d, 6.8 Hz, 2H), 7.33–7.21 (m, 4H), 7.06 (d, 8.1 Hz, 1H), 5.28 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.3, 152.1, 138.5, 136.9, 135.1, 128.9, 128.6, 128.5, 127.7, 123.5, 114.9, 114.7, 44.2.

4-Benzyl-1-(2-nitrobenzoyl)-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione (15).

Triethylamine (0.303 g, 3 mmol) was added to a solution of benzodiazepinedione **12** (0.532 g, 2.0 mmol) in dry CH_2Cl_2 (40 mL). The resulting mixture was stirred for 15 min and then treated with DMAP (0.244 g, 2.0 mmol). Freshly prepared 2-nitrobenzoyl chloride (0.557 g, 3.0 mmol) in dry CH_2Cl_2 (2 mL) was added drop-wise to the solution and the resulting mixture was stirred for 2 h at room temperature. The solution was washed with water (3x40 mL), dried and concentrated. The residue was purified on a silica gel column (35% ethyl acetate in hexane) to afford **15** (0.406 g). Yield: 49%, mp 168–169 °C. FT IR (KBr) 1740 ($\nu_{C=O}$), 1710 ($\nu_{C=O}$), 1642 ($\nu_{C=O}$), 1600, 1519, 1459, 1346 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (d, 7.9 Hz, 1H), 7.99 (dd, 1.5 Hz, 7.7 Hz, 1H), 7.74 (d, 7.3 Hz, 1H), 7.68–7.53 (m, 4H), 7.30 (s, 5H), 7.01 (dd, 1.5 Hz, 7.5 Hz, 1H), 4.85 (d, 14.6 Hz, 1H), 4.72 (d, 14.6 Hz, 1H), 4.12 (d, 15.7 Hz, 1H), 3.62 (d, 15.7 Hz, 1H).

***N*-Benzylsclerotigenin (17).**

A solution of **15** (0.112 g, 0.27 mmol) in ethyl acetate (12 mL) in the presence of Pd/C (10%) was stirred at 50 °C under pressure of hydrogen balloon until the reaction was completed. The reaction mixture was filtered over band of celite, evaporated and purified by a silica gel column (30–35% ethyl acetate in hexane) to furnish *N*-benzylscleroteginin **17** (76 mg). Yield: 77%, mp 173–174 °C. FT IR (KBr): 1697 ($\nu_{C=O}$), 1610 ($\nu_{C=O}$), 1593 ($\nu_{C=N}$), 1465, 1142 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (d, 7.9 Hz, 1H), 8.02 (d, 7.9 Hz, 1H), 7.79 (m, 1H), 7.67–7.51 (m, 5H), 7.37–7.22 (m, 5H), 5.37 (d, 14.8 Hz, 1H), 4.35 (d, 14.8 Hz, 1H), 4.32 (d, 15.00 Hz), 4.13 (d, 15.00 Hz); MS (EI) m/z (relative intensity %): 367.5 (M^+ ($C_{23}H_{17}O_2N_3$), 62), 261.4 (100), 235.4 (66), 91.2 (54). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 161.2, 152.2, 146.3, 136.2, 134.9, 133.6, 131.1, 131.0, 130.6, 128.9, 128.8, 128.4, 127.9, 127.7, 127.7, 127.6, 127.5, 121.6, 51.9, 50.4. Anal. Calcd. for $C_{23}H_{17}O_2N_3$: C 75.19, H 4.66, N 11.44. Found: C 74.91, H 4.55, N 11.53.

Acknowledgements

We thank the Deanship of Research at Jordan University of Science and Technology for financial support, Grant No.7/2000. We also thank Deeb T. Deeb for assistance in doing some spectroscopic data.

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Povzetek

N-Benzilsklerotigenin smo sintetizirali v štirih stopnjah. Anhidrid izatojske kisline je reagiral najprej z benzilaminom, nato pa še kloroacetil kloridom. Nastali dipeptid smo ciklizirali v [1,4]benzodiazepindion. Tega smo acilirali z o-nitrobenzoil kloridom v labilni derivat, ki smo ga nato reducirali v *N*-benzilsklerotigenin z dobrim izkoristkom. To metodologijo lahko uporabimo v kombinatorni sintezi knjižnice *N*-substituiranih kinazolino[1,4] benzodiazepindionov za biološko vrednotenje.