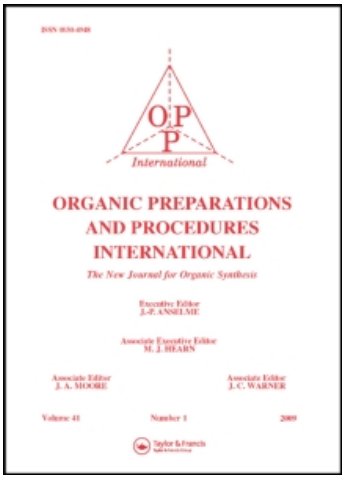

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PREPARATION OF 5,10,11,11a-TETRAHYDRO-1*H*, 3*H*-THIAZOLO[2,3-*c*]- AND 5,10,11,11a-TETRAHYDRO-1*H*, 3*H*-THIAZOLO[4,3-*c*]-[1,4]BENZODIAZEPINES

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PREPARATION OF 5,10,11,11a-TETRAHYDRO-1*H*,3*H*-THIAZOLO[2,3-*c*]- AND 5,10,11,11a-TETRAHYDRO-1*H*,3*H*-THIAZOLO[4,3-*c*]-[1,4]BENZODIAZEPINES

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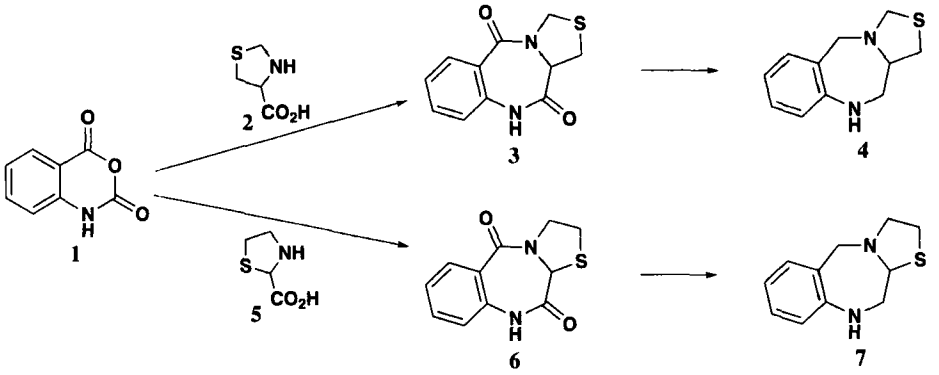
Benzodiazepines are perceived as "privileged" heterocyclic scaffolds for the genesis of drug candidates because this subunit tends to confer interesting biological activity to molecules.[1-7] For example, benzodiazepines are important components of anxiolytics,[1] vasopressin receptor antagonists,[2,3] non-opioid analgesics,[4] and cholecystokinin receptor antagonists.[5] Additionally, pyrrolo[1,4] benzodiazepine antibiotics have attracted attention as potent anticancer agents.[6] Although the syntheses of a variety of benzodiazepines are well documented, preparations of heterocyclic systems **4** and **7** are unknown. Since we needed intermediates **4** and **7** for a medicinal chemistry project, we developed convenient synthetic methods, which are reported herein.



The main synthetic approaches to amino acid-derived tricyclic benzodiazepinediones are based on acylation of a cyclic amino acid ester with *o*-nitrobenzoyl chloride, followed by tandem reduction-cyclization reaction,[8-10] or on condensation of proline with isatoic anhydride.[8-10] Previously, Carabateas[8-10] reported the preparation of **3** in 48% yield by using the first route. However, our synthesis is based on the latter synthetic approach. One challenge in the synthesis of benzodiazepinediones **3** and **6** is the acid sensitivity of the starting materials and final products. To overcome this difficulty, we performed the condensation in a 4:1 mixture of dimethylformamide (DMF) and triethylamine (TEA). We found that heating a 1:1 mixture of isatoic anhydride and thiazolidinecarboxylic acids **2** and **5** in DMF-TEA affords moderate yields of benzodiazepinone **3** or **6**, respectively, in a simple reaction work-up. Our attempts to perform this reaction in either DMF or pyridine resulted in a

mixture of products. The benzodiazepinediones **3** and **6** were reduced to the corresponding amines **4** and **7** in good yields with lithium aluminum hydride in THF at 0°.

Starting with (-)-(*R*)-thiazolidine-4-carboxylic acid, enantiomerically pure **4** was prepared.[11] Substituted isatoic anhydrides (like 5-chloroisatoic anhydride) produced tricyclic benzodiazepindiones with approximately the same yield as that obtained with **1**. Our attempts to prepare derivatives of 2,2-dimethylthiazolidine-4-carboxylic acid were unsuccessful.

EXPERIMENTAL SECTION

Mps were determined using Thomas-Hoover capillary melting point apparatus and are uncorrected. All chemicals and solvents were obtained from commercial sources and used without purification. ^{1}H and ^{13}C NMR spectra were collected on Bruker AC-300 NMR spectrometer; chemical shifts are reported with tetramethylsilane as an internal reference ($\delta_{H,C}$ = 0.0 ppm). Spectra were acquired at ambient temperature in DMSO-d_6 or $CDCl_3$. Mass spectral analyses were performed on a Fisons instrument (Hewlett-Packard HPLC driven electrospray MS instrument). Analytical HPLC analyses were performed on a Hewlett-Packard liquid chromatography system (YMC column, 4 mm x 50 mm, 4 μm C_{18}, 1.0 mL/min, 8 min gradient from 95% aqueous media (0.1% TFA) to 95% CH_3CN (0.1% TFA), monitoring wavelength 220 and 260 nm).

General Procedure for Compounds 3 and 6.- A solution of thiazolidine carboxylic acid (1.33 g, 10 mmol) and isatoic anhydride (1.63 g, 10 mmol) in 15 mL of a 4:1 (v/v) mixture of DMF:TEA was heated in a sealed tube for 2 h at 120°. The reaction mixture was cooled to room temperature and poured into cold water (300 mL), and the mixture was stirred for 2 hr. The white solid was collected, washed with water, and dried in a vacuum oven to provide benzodiazepinedione **3** (1.29 g, 55%). The compound was homogeneous by NMR and HPLC; analytically pure material was obtained by crystallization from methyl *t*-butyl ether.

Compound **3**: white crystals (from methyl *t*-butyl ether), mp. 208-210° (dec.); MS *m/z* 235 (M+H); NMR (300 MHz, DMSO-d_6) 10.6 (s, 1H), 7.80 (d, *J* = 7 Hz, 1H), 7.55 (t, *J* = 7 Hz, 1H), 7.25 (t, *J* = 8 Hz, 1H), 7.16 (d, *J* = 8 Hz, 1H), 4.67 (dd, *J* = 2, 10 Hz, 2H), 4.45 (dd, *J* = 2, 7 Hz, 1H), 3.60 (dd, *J* =12, 3 Hz, 1H), 3.24 (dd, *J* = 5, 3 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) 169.9, 164.5, 136.7, 132.9, 130.9, 126.0, 124.3, 121.6, 58.5, 50.1, 31.1.

Anal. Calcd for $C_{11}H_{10}N_2O_2S$: C, 56.39; H, 4.30; N, 11.96. Found: C, 56.24; H, 4.53; N, 11.83

Since compound **6** did not precipitate from aqueous solution upon stirring, it was extracted into ether (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and evaporated. The brown solid residue was recrystallized from methyl *t*-butyl ether to provide **6** (0.70 g, 30%).

Compound **6**: white crystals (from methyl *t*-butyl ether), mp. 248-251° (dec.); MS *m/z* 235 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6) 7.79 (d, *J* = 8 Hz, 1H), 7.54 (t, *J* = 6 Hz, 1H), 7.25 (t, *J* = 8 Hz, 1H), 7.14 (d, *J* = 8 Hz, 1H), 5.41 (s, 1H), 4.01-3.92 (m, 1H), 3.81-3.71 (m, 1H), 3.15-3.10 (m, 1H), 3.08-2.95 (m, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) 167.6, 164.2, 136.8, 132.8, 130.8, 126.5, 124.4, 121.7, 62.7, 50.6, 29.2.

Anal. Calcd for $C_{11}H_{10}N_2O_2S$: C, 56.39; H, 4.30; N, 11.96. Found: C, 56.25; H, 4.20; N, 11.87

General Procedure for Compounds 4 and 7.- To a solution of benzodiazepinedione (**3** or **6**, 1.17 g, 5 mmol) in 50 mL of dry THF, cooled in an ice bath, was added dropwise $LiAlH_4$ (1.0 M in THF, 2.5 mL, 2.1 equiv) and the reaction mixture was heated to reflux. After 8 h, the solution was cooled to room temperature, and quenched by the sequential addition of 0.4 mL of water, 0.4 mL of 1 N NaOH, and 1.2 mL of water (**CAUTION**). The reaction mixture was filtered through Celite® and the filtrate was evaporated. The yellow solid concentrate was subjected to flash column chromatography (ethyl acetate) to provide the benzodiazepine **4** (80%) or **7** (65%).

Compound **4**: white crystals (from methyl *t*-butyl ether), mp.225-228° (dec.), *lit.*[9] (from $CHCl_3$-EtOH) mp 235.5-237°; MS *m/z* 207 (M+H); NMR (300 MHz, $CDCl_3$) 7.13-7.08 (m, 2H), 6.85 (t, J = 7 Hz, 1H), 6.72 (d, J = 8 Hz, 1H), 4.14-4.04 (m, 3H), 3.82 (broad s., 1H), 3.51 (d, J = 14 Hz, 1H), 3.41 (dd, J = 4, 10 Hz, 1H), 3.20-3.00 (m, 2H), 2.99-2.88 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) 151.3, 130.5, 127.8, 127.7, 119.4, 118.3, 69.6, 60.8, 55.6, 48.9, 32.3.

Anal. Calcd for $C_{11}H_{14}N_2S$: C, 64.04; H, 6.84; N, 13.58. Found: C, 63.88; H, 6.85; N, 13.44

Compound **7**: white crystals (from methyl *t*-butyl ether), mp.112-115°; MS *m/z* 207 (M+H); ^1H NMR (300 MHz, $CDCl_3$) 6.93 (dd, J = 13, 7 Hz, 2H), 6.80 (t, J = 7 Hz, 1H), 6.68 (d, J = 8 Hz, 1H), 4.50 (dd, J = 10, 4 Hz, 1H), 4.25 (d, J = 14 Hz, 1H), 3.97 (broad s, 1H), 3.51-3.29 (m, 4H), 3.10-2.90 (m, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) 149.9, 130.3, 127.6, 125.9, 118.4, 117.6, 74.7, 59.8, 54.2, 49.3, 30.7.

Anal. Calcd for $C_{11}H_{14}N_2S$: C, 64.04; H, 6.84; N, 13.58. Found: C, 64.00; H, 6.63; N, 13.55

REFERENCES

1. W. Hunkeler, E. Kuburz, Eur. Patent 195939 1986; *Chem. Abstr.*, **106**:84659 (1987).

2. Y. Ohtake, A. Naito, H. Hasegawa, K. Kawano, D. Morizono, M. Taniguchi, Y. Tanaka, H. Matsukawa, K. Naito, T. Oguma, Y. Ezure, Y. Tsuriya, *Bioorg. Med. Chem. Lett.*, **7**, 1247 (1999).

3. W. J. Hoekstra, A. B. Dyatkin, B. E. Maryanoff and J. M. Matthews, Patent WO 0043398 (1999); *Chem. Abstr.*, **133**:120350 (2000).

4. J. MacDonald, J. Matz, W. Shakespeare, Patent WO 9717344 (1996); *Chem. Abstr.*, **127**:50549 (1997).

5. B. E. Evan, M. G. Bock, *Adv. Med. Chem.*, **2**, 111 (1993)

6. D. E. Thurston, D. S. Bose, *Chem. Rev.*, **94**, 433 (1994)

7. B. Refouvelet, P. Tronche, J. Couquelet, J. F. Robert, G. Bonnefoy-Claudet, J. Panouse-Perrin, *Eur. J. Med. Chem.*, **22**, 11 (1987).

8. P. M. Carabateas, US Patent 3,860,600, 1975; *Chem. Abstr.*, **83**:58892 (1975).

9. P. M. Carabateas, US Patent 3,732,212, 1973; *Chem. Abstr.*, **79**:42570 (1973).

10. P. M. Carabateas, US Patent 3,763,183, 1973; *Chem. Abstr.*, **79**:546567 (1979).

11. The enantiomeric purity was determined by ^{1}H NMR with (+)-(*S*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol as a chiral solvent. The corresponding (*R*)-enantiomer had $[\alpha]_D^{20}$ -113.8° (*c* 0.488, CH_2Cl_2).

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FACILE PREPARATION OF *trans*-2,3-bis(-*tert*-BUTYLAMINOMETHYL) NORBORNENE

Submitted by J. H. Wynne[†,††] and W. M. Stalick*[†]
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Norbornenes possessing sterically hindered amino pendant groups are a class of compounds used in the synthesis of novel advanced organic materials.[1] Polymers bearing amino and different heteroatom pendant groups are typically synthesized because they are able to chelate metals.[2] In addition, polymerization of compound **3**, where the bulky amino substituents are *t*-butyl groups, readily affords a material with a rigid backbone containing amine groups which have been shown to chelate to metals such as zinc and copper.[3] These molecules have also been employed in polymers for their non-linear optical properties.[3,4] The synthesis of diaminomethyl norbornene **3** has been reported in the literature albeit in only low to moderate yields.[5] This lengthy four-step procedure involves a Diels-Alder reaction between cyclopentadiene and fumaric acid, followed by reduction to the *trans*-diol, subsequent treatment of the diol with tosyl chloride in pyridine to give the ditosylate, which upon reaction with *t*-butylamine in DMF at 100° for prolonged periods, in a sealed reaction vessel, resulted in the desired product **3**. This typically used method requires the use of a specialized reaction vessel at elevated temperature and pressure. We now report that compound **3** can be easily synthesized in high yields by a very simple facile approach resulting in both high purity and yields.

Treatment of freshly cracked cyclopentadiene, with *trans*-fumaronitrile afforded the Diels-Alder adduct **1** in quantitative yields as previously reported.[6] Subsequent treatment under Ritter-type reaction conditions, employing *t*–butyl alcohol and conc. sulfuric in acid glacial acetic acid, transformed **1** to the di-*t*-butylamide **2**. This facile transformation can be performed in an Erlenmeyer flask and requires no inert atmosphere or special equipment. However, it is imperative that the temperature be maintained between 0 to 50° in order to prevent both ester and ether formation, which results if the temperature is not controlled.