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A Short and Efficient Synthesis of Novel N-(2,3-dihydro-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl)-2-carboxamides

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Summary. Several novel N-(2,3-dihydro-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl)-2-carboxamides were prepared by acyl coupling of 2-aminobenzophenones with α-(benzotriazol-1-yl)-N-acylglycines followed by displacement of the benzotriazole ring with ammonia and cyclization of the resulting monoacyl aminals. In addition to high yields and shorter reaction sequences due to avoiding deprotection and acylation of the protected 3-amino-1,4-benzodiazepin-2-one intermediates, the present approach did not involve the use of toxic and odoriferous materials as is the case with other methods.

Keywords. 3-Substituted 1,4-benzodiazepin-2-ones; α-(Benzotriazol-1-yl)-N-acylglycines; Cholecystokinin antagonists.

Introduction

Since the isolation and identification of asperlicin [1] as a non-peptide antagonist of the peptide hormone cholecystokinin (*CCK*), various 3-substituted benzodiazepines have been designed as agonists and/or antagonists of the peripheral (*CCK*-A) and/or central (*CCK*-B) receptor subtypes [2–4]. The development of devazepide [5], FK 480 [3], *etc*. as *CCK*-A antagonists for the treatment of pancreatitis, irritable bowel syndrome, and pancreatic cancer [3] and *CCK*-A agonists such as GW 5823 for the suppression of food intake [2] have demonstrated the significance of these investigations. These potent compounds, which display both high selectivity and good oral activity, are currently under clinical investigations [2–3]. In connection with ongoing work aimed at the synthesis and evaluation of novel N-(2,3-dihydro-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl)-2-carboxamides as *CCK*-A antagonists and in view of problems and limitations associated with the preparation of analogous compounds, a general convenient synthesis of the title compounds is reported in this paper.

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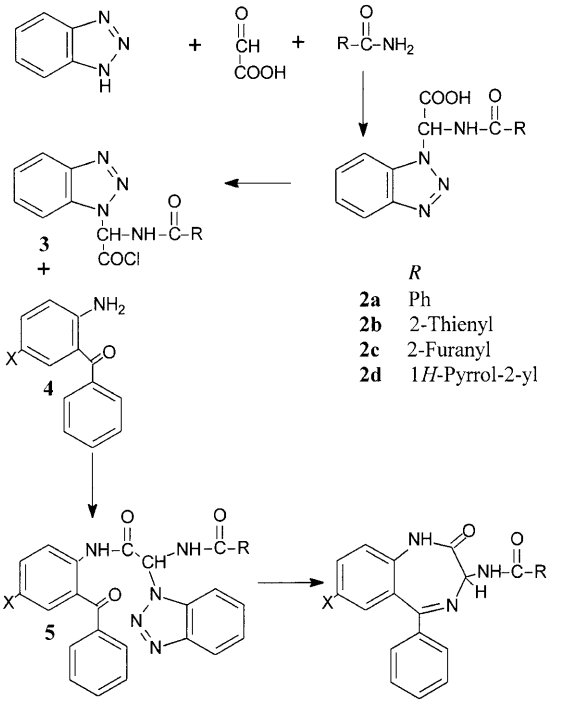
[a] Part of PhD thesis

Results and Discussion

3-(Acylamino)-5-phenyl-2*H*-1,4-benzodiazepin-2-ones are usually prepared by acylation of 3-amino-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**1**) either with acyl chlorides or with free acids in the presence of a coupling agent such as 1-(3-(dimethylamino)-propyl)-3-ethylcarbodiimide hydrochloride (*EDC*)[6]. Reported methods for the synthesis of **1** are based on the preparation and transformation of benzodiazepine-N-oxide [7–8], elimination-addition reactions of 2-(N-acetoxyacetamido)-2′-benzoylacetanilide [9–10], construction of the N^1-substituted 1,4-benzodiazepine nucleus followed by introduction of the 3-amino group [11], acyl coupling of α-(isopropylthio)- or α-(benzotriazol-1-yl)-N-(benzyloxycarbonyl)-glycine with 2-aminobenzophenone followed by displacement of the α-substituent with ammonia, cyclization of the resulting protected monoacyl aminal, and removal of the blocking group [11–12]. These methods suffer from a number of drawbacks including low yields and/or lengthy reaction sequences [7–10], inadequacy for large scale preparations [6], use of highly toxic and odoriferous materials [11], and protection/deprotection steps [11–12].



Scheme 1

In the course of our investigations on the design and synthesis of the *CCK*-A antagonists, a shorter and more efficient reaction sequence for the preparation of novel N-(2,3-dihydro-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl)-2-carboxamides **6a–g** was developed through installing the desired acyl group of the final product as a protecting group of α-(benzotriazol-1-yl)-glycine. The novel α-(benzotriazol-1-yl)-N-acylglycine synthons **2a–d** were prepared by condensation of benzotriazole, glyoxylic acid, and the corresponding amides with azeotropic removal of water [13]. Acyl coupling of these new synthons with 2-aminobenzophenones **4** and subsequent displacement of the benzotriazole moiety with ammonia followed by cyclization of the resulting amino ketone intermediate **5** (Scheme 1) gave the desired 3-substituted benzodiazepines **6a–g**.

By the synthetic sequences described, the known compound **6a** [14] was prepared in 77% overall yield, whereas the novel compounds **6b–g** were obtained in 59–72% overall yield. A major advantage of the present approach, which was developed by the modification of the published procedures for the preparation of analogous 3-substituted 1,4-benzodiazepin-2-ones [11–12], is shortening the synthetic route from five to three steps by eliminating the deprotection and acylation of the protected 3-aminobenzodiazepinone intermediates. The biological activities of **6b–g** are currently under investigation.

Experimental

Melting points were determined on a Reichert hot plate apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity Plus 400 spectrometer (399.866 MHz for ^{1}H NMR and 100.556 MHz for ^{13}C NMR) using *DMSO*-d_6 as solvent. Chemical shifts (δ) are reported in ppm relative to *TMS* as internal standard. Mass spectra were obtained on a Finnigan TSQ-70 instrument. Infrared spectra were recorded on a Nicolet Magna IR 550 spectrometer.

General procedure for the preparation of α-(benzotriazol-1-yl)-N-acylglycines **2a–d**

Benzotriazole (2.38 g, 20 mmol), 1.84 g glyoxylic acid monohydrate (20 mmol), and 20 mmol of the appropriate amide in 100 cm^3 toluene were refluxed in a *Dean-Stark* apparatus for 3 h. Compounds **2a** and **2b** which precipitated upon cooling were purified by washing with ether, crystallization from methanol/ether, and drying under high vacuum. For isolation of compounds **2c** and **2d**, the reaction mixture was cooled to room temperature, the solvent was decanted, and the residue was triturated with 5 cm^3 of methanol. The resulting precipitates were purified by crystallization from methanol/ether.

2-(1H-Benzotriazol-1-yl)-2-(benzoylamino)acetic acid (**2a**; $C_{15}H_{12}N_4O_3$)

Yield: 5.44 g (92%); m.p.: 195–197°C; ^{1}H NMR (400 MHz): $\delta = 7.42$ (t, 1H, $J = 7.6$ Hz), 7.47–7.52 (m, 3H), 7.56–7.60 (m, 2H), 7.91–7.94 (m, 2H), 8.05–8.12 (m, 2H), 10.17 (d, 1H, $J = 7.6$ Hz) ppm; ^{13}C NMR (100 MHz): $\delta = 63.87$, 111.54, 119.21, 124.24, 127.76, 127.85, 128.51, 132.33, 132.68, 145.19, 166.80, 167.12 ppm; IR (KBr): $\nu = 1150$, 1277, 1523, 1659, 1722, 3323 cm^{-1}; MS (70 eV): $m/z = 296$ (M^+).

2-(1H-Benzotriazol-1-yl)-(2-thienylamino)acetic acid (**2b**; $C_{13}H_{10}N_4O_3S$)

Yield: 5.31 g (88%); m.p.: 205–207°C; ^{1}H NMR (400 MHz): $\delta = 7.20$ (t, 1H, $J = 4$ Hz), 7.44 (t, 1H, $J = 7.6$ Hz), 7.56 (d, 1H, $J = 4$ Hz), 7.60 (t, 1H, $J = 7.6$ Hz), 7.87 (d, 1H, $J = 8$ Hz), 8.05 (d, 1H,

$J = 7.6$ Hz), 8.07 (d, 1H, $J = 4$ Hz), 8.09 (d, 1H, $J = 7.6$ Hz), 10.31 (d, 1H, $J = 8$ Hz) ppm; ^{13}C NMR (100 MHz): $\delta = 63.69$, 111.52, 119.19, 124.23, 127.69, 128.32, 130.24, 132.25, 132.70, 137.62, 145.13, 161.44, 166.92 ppm; IR (KBr): $\nu = 1156$, 1402, 1549, 1622, 1759, 3218 cm^{-1}; MS (70 eV): $m/z = 302$ (M^+).

2-(1H-Benzotriazol-1-yl)-2-(2-furanylamino)acetic acid (**2c**: $C_{13}H_{10}N_4O_4$)

Yield: 4.63 g (81%); m.p.: 185–187°C; ^{1}H NMR (400 MHz): $\delta = 6.65$ (dd, 1H, $J = 1.6$ Hz, $J = 0.8$ Hz), 7.35 (dd, 1H, $J = 1.6$ Hz, $J = 0.4$ Hz), 7.42 (t, 1H, $J = 7.6$ Hz), 7.47 (d, 1H, $J = 8$ Hz), 7.57 (t, 1H, $J = 7.6$ Hz), 7.90 (dd, 1H, $J = 0.8$ Hz, $J = 0.4$ Hz), 8.06 (t, 2H, $J = 7.6$ Hz), 10.08 (d, 1H, $J = 8$ Hz) ppm; ^{13}C NMR (100 MHz): $\delta = 63.39$, 111.69, 112.37, 115.96, 119.30, 124.45, 127.88, 132.30, 145.29, 146.19, 146.52, 157.97, 166.94 ppm; IR (KBr): $\nu = 1406$, 1655, 1733, 3144 cm^{-1}; MS (70 eV): $m/z = 286$ (M^+).

2-(1H-Benzotriazol-1-yl)-(1H-pyrrol-2-ylamino)acetic acid (**2d**; $C_{13}H_{11}N_5O_3$)

Yield: 4.16 g (73%); m.p.: 195–196°C; ^{1}H NMR (400 MHz): $\delta = 7.07$ (t, 1H, $J = 4$ Hz), 7.35 (t, 1H, $J = 7.6$ Hz), 7.41 (d, 1H, $J = 8$ Hz), 7.49 (t, 1H, $J = 7.6$ Hz), 7.62 (d, 1H, $J = 4$ Hz), 7.80 (br, 1H), 7.96 (d, 1H, $J = 4$ Hz), 7.99–8.02 (m, 2H), 10.02 (d, 1H, $J = 8$ Hz) ppm; ^{13}C NMR (100 MHz): $\delta = 63.48$, 111.18, 118.92, 123.80, 127.28, 127.70, 130.15, 131.72, 132.12, 137.55, 145.15, 161.42, 166.64 ppm; IR (KBr): $\nu = 1408$, 1659, 1749, 3176 cm^{-1}; MS (70 eV): $m/z = 285$ (M^+).

General procedure for the preparation of N-(2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-2-carboxamides **6a–g**

Oxalyl chloride (0.86 cm^3, 10 mmol) and 0.1 cm^3 anhydrous *DMF* were added to a solution of 10 mmol of **2** in 40 cm^3 of anhydrous *THF* under N_2 at 0–5°C, and the mixture was stirred below 5°C for 2 h. A solution of 1.97 g 2-aminobenzophenone (10 mmol) and 2.1 cm^3 anhydrous N-methylmorpholine in 15 cm^3 of anhydrous *THF* was added to the stirred mixture at 5°C over 30 min; thereafter, the reaction mixture was allowed to reach room temperature. The reaction slurry was filtered, and the mother liquor was saturated with ammonia gas, diluted with 80 cm^3 of methanol, and again saturated with ammonia gas for approximately 30 min. After evaporation of the solvent under reduced pressure, the residue was dissolved in 50 cm^3 of ethyl acetate, washed successively with 1 *N* aqueous NaOH solution and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Following the treatment of the resulting crude amino ketone intermediate with a solution of 3.3 g ammonium acetate in 40 cm^3 glacial acetic acid, the reaction solution was stirred under N_2 overnight. The solvent was evaporated under reduced pressure, the residue was suspended in 10 cm^3 ethyl acetate and 50 cm^3 diethyl ether, and the *pH* of the mixture adjusted to approximately 8.5 by addition of 1 *N* aqueous NaOH solution. The crude products, which precipitated upon cooling the suspension, were crystallized from ethyl acetate/diethyl ether to give the pure compounds **6a–g**.

N-(2,3-Dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-benzamide (**6a**; $C_{22}H_{17}N_3O_2$)

Yield: 2.73 g (77%); m.p.: 233–235°C; ^{1}H NMR (400 MHz): $\delta = 5.21$ (d, 1H, $J = 6.8$ Hz), 7.03–7.25 (m, 3H), 7.43–7.58 (m, 9H), 7.99 (d, 2H, $J = 6.8$ Hz), 9.27 (d, 1H, $J = 6.8$ Hz) ppm; ^{13}C NMR (100 MHz): $\delta = 68.49$, 120.17, 122.73, 125.71, 126.68, 127.65, 127.91, 129.03, 129.57, 129.74, 130.82, 131.05, 133.55, 138.36, 143.77, 165.52, 165.67, 166.48 ppm; IR (KBr): $\nu = 523$, 770, 1260, 1383, 1527, 1660, 1705, 2889, 3319, 3462 cm^{-1}; MS (70 eV): $m/z = 355$ (M^+).

N-(2,3-Dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-thiophen-2-carboxamide (**6b**; $C_{20}H_{15}N_3O_2S$)

Yield: 2.67 g (74%); m.p.: 219–221°C; ^{1}H NMR (400 MHz): $\delta = 5.48$ (d, 1H, $J = 7.6$ Hz), 7.20 (t, 1H, $J = 4$ Hz), 7.24–7.36 (m, 3H), 7.44–7.54 (m, 6H), 7.63–7.67 (m, 1H), 7.81 (d, 1H, $J = 5.2$ Hz), 9.64 (d, 1H, $J = 7.6$ Hz) ppm; ^{13}C NMR (100 MHz): $\delta = 68.91$, 121.42, 123.25, 126.30, 128.06, 128.14, 128.29, 129.49, 130.58, 131.42, 131.54, 132.21, 138.12, 138.82, 139.22, 161.19, 167.16, 168.02 ppm; IR (KBr): $\nu = 707$, 1178, 1271, 1501, 1650, 1696, 2889, 3088, 3329 cm^{-1}; MS (70 eV): $m/z = 361$ (M^+).

N-(2,3-Dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-furan-2-carboxamide (**6c**; $C_{20}H_{15}N_3O_3$)

Yield: 2.28 g (66%); m.p.: 207–209°C; ^{1}H NMR (400 MHz): $\delta = 5.69$ (d, 1H, $J = 8$ Hz), 6.51 (dd, 1H, $J = 3.6$ Hz, $J = 1.6$ Hz), 7.13–7.24 (m, 3H), 7.32–7.36 (m, 3H), 7.41–7.54 (m, 5H), 8.15 (d, 1H, $J = 8$ Hz) ppm; ^{13}C NMR (100 MHz): $\delta = 67.04$, 112.00, 114.97, 121.56, 123.82, 127.40, 128.05, 129.79, 130.45, 131.16, 132.02, 137.64, 138.59, 144.41, 147.50, 158.11, 168.31, 168.64 ppm; IR (KBr): $\nu = 523$, 764, 1189, 1378, 1511, 1647, 1706, 2361, 2889, 3155, 3406 cm^{-1}; MS (70 eV): $m/z = 345$ (M^+).

N-(2,3-Dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-1H-pyrrol-2-carboxamide (**6d**; $C_{20}H_{16}N_4O_2$)

Yield: 2.03 g (59%); m.p.: 212–214°C; ^{1}H NMR (400 MHz): $\delta = 5.36$ (d, 1H, $J = 6.8$ Hz), 5.58 (d, 1H, $J = 8.4$ Hz), 7.03–7.10 (m, 3H), 7.45–7.55 (m, 7H), 7.58 (d, 1H, $J = 3.6$ Hz), 7.66 (d, 1H, $J = 6.8$ Hz) ppm; ^{13}C NMR (100 MHz): $\delta = 62.10$, 127.88, 127.95, 128.96, 129.14, 129.38, 130.88, 131.24, 131.41, 137.74, 137.84, 142.46, 162.13, 162.24, 169.12, 169.55 ppm; IR (KBr): $\nu = 704$, 1122, 1429, 1542, 1614, 1650, 1745, 2361, 3176, 3360 cm^{-1}; MS (70 eV): $m/z = 344$ (M^+).

3-(Benzoylamino)-7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (**6e**; $C_{22}H_{16}ClN_3O_2$)

Yield: 2.80 g (72%); m.p.: 217–219°C; ^{1}H NMR (400 MHz): $\delta = 5.39$ (d, 1H, $J = 7.2$ Hz), 7.26–7.31 (m, 2H), 7.46–7.60 (m, 9H), 8.17 (d, 2H, $J = 7.6$ Hz), 9.42 (d, 1H, $J = 7.2$ Hz) ppm; ^{13}C NMR (100 MHz): $\delta = 69.14$, 123.79, 126.49, 127.62, 127.78, 128.29, 128.38, 129.47, 130.69, 131.62, 131.97, 133.63, 137.86, 138.94, 165.65, 166.31, 167.58 ppm; IR (KBr): $\nu = 530$, 702, 835, 1393, 1481, 1657, 1699, 2955, 3473 cm^{-1}; MS (70 eV): $m/z = 389$ (M^+).

7-Chloro-1,3-dihydro-5-phenyl-3-(2-thienylcarbonylamino)-2H-1,4-benzodiazepin-2-one (**6f**; $C_{20}H_{14}ClN_3O_2S$)

Yield: 2.76 g (70%); m.p.: 173–175°C; ^{1}H NMR (400 MHz): $\delta = 5.69$ (d, 1H, $J = 7.6$ Hz), 7.11–7.14 (m, 2H), 7.35–7.54 (m, 8H), 7.73 (d, 1H, $J = 3.6$ Hz), 7.78 (d, 1H, $J = 7.6$ Hz) ppm; ^{13}C NMR (100 MHz): $\delta = 67.66$, 123.13, 127.81, 128.37, 128.71, 129.03, 129.79, 130.65, 130.85, 132.35, 133.12, 136.09, 136.15, 137.88, 161.74, 167.30, 168.54 ppm; IR (KBr): $\nu = 532$, 702, 1281, 1490, 1537, 1644, 1706, 2356, 2930, 3416 cm^{-1}; MS (70 eV): $m/z = 395$ (M^+).

7-Chloro-1,3-dihydro-3-(2-furanylcarbonylamino)-5-phenyl-2H-1,4-benzodiazepin-2-one (**6g**; $C_{20}H_{14}ClN_3O_3$)

Yield: 2.35 g (62%); m.p.: 164–166°C; ^{1}H NMR (400 MHz): $\delta = 5.70$ (d, 1H, $J = 8$ Hz), 6.54 (dd, 1H, $J = 3.6$ Hz, $J = 1.6$ Hz), 7.16–7.21 (m, 2H), 7.37–7.55 (m, 8H), 8.03 (d, 1H, $J = 8$ Hz) ppm;

^{13}C NMR (100 MHz): $\delta = 67.13$, 112.15, 115.15, 123.07, 128.44, 128.86, 129.80, 130.70, 130.96, 132.38, 136.14, 137.98, 144.52, 147.55, 158.10, 167.09, 168.29 ppm; IR (KBr): $\nu = 513$, 810, 1020, 1404, 1573, 1650, 1706, 2361, 3457 cm^{-1}; MS (70 eV): $m/z = 379$ (M^+).

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