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Facile Synthesis of Dihydro-1,2,4-benzotriazepin-5-ones

Nisreen I. Hindawi[1], **Jalal A. Zahra**[1], **Mustafa M. El-Abadelah**[1,*], **Bassam A. Abu Thaher**[2], and **Klaus-Peter Zeller**[3]

[1] Chemistry Department, Faculty of Science, University of Jordan, Amman, Jordan
[2] Chemistry Department, Faculty of Science, Islamic University of Gaza, Gaza Strip
[3] Institut für Organische Chemie, Universität Tübingen, Tübingen, Germany

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Summary. Direct interaction between model anilines and an 1,3-dipolar nitrile imine, derived from 2-[*N*′-(1-chloro-2-oxopropylidine)hydrazine]benzoic acid, yielded the respective acyclic amidrazones. The latter adducts underwent *CDI*-induced cyclocondensation involving the hydrazone–NH terminus and the activated carboxy group to produce the corresponding dihydro-1,2,4-benzotriazepin-5-ones.

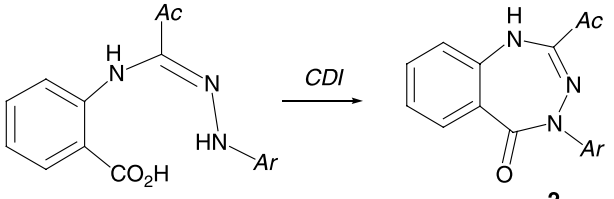
Keywords. *N*-(2-Carboxyphenyl)hydrazonoyl chloride; 1,3-Nucleophilic addition; *N*-Arylamidrazones; Cyclization; Dihydro-1,2,4-benzotriazepin-5-ones.

Introduction

Recently, we have reported on a facile synthesis of model 1,4-dihydro-1,3,4-benzotriazepin-5-ones **2** *via* cyclocondensation of the respective *N*-arylamidrazone precursors **1**, induced by 1,1′-carbonyldiimidazole (*CDI*) (Scheme 1) [1–3]. The latter acyclic adducts **1** are readily accessible by direct interaction of anthranilic acid with the appropriate hydrazonoyl chloride in the presence of triethylamine [1–3].

Following this route, we envisaged that the isomeric dihydro-1,2,4-benzotriazepin-5-ones **5** would be similarly prepared *via* a *CDI*-induced lactamization of *N*-arylamidrazones **4** (accessible from interaction of **3** and $Ar\text{NH}_2$), whereby anthranilic acid is already incorporated as part of their hydrazone moiety (Scheme 2). As outlined in the latter scheme, this expectation is realized in the present study, which deals with the synthesis and characterization of model dihydro-1,2,4-benzotriazepinones **5a**–**5c** and their acyclic amidrazone precursors **4a**–**4c**.

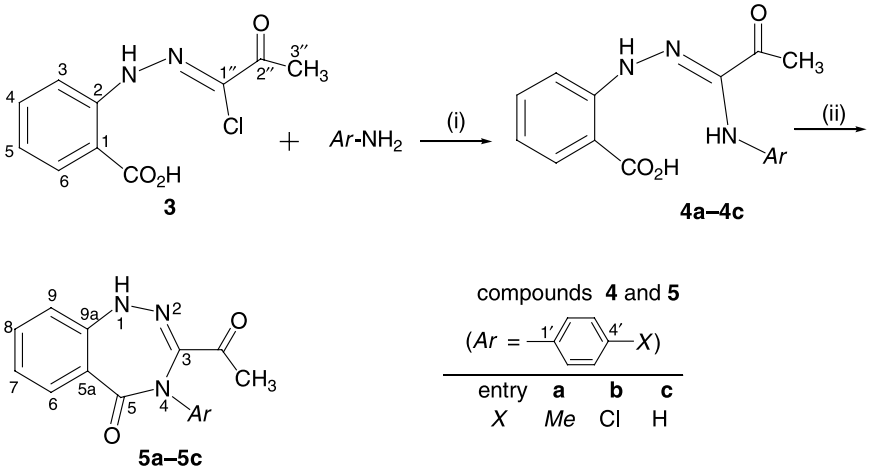
* Corresponding author. E-mail: mustelab@ju.edu.jo



1 **2**

(*Ar* = *Ph*, *p*-*Me*C_6H_4, *p*-ClC_6H_4)

Scheme 1



3 **4a–4c** **5a–5c**

(i) *THF* + *Me*OH, N*Et*$_3$ / 0 ⟶ 20°C, 6–8 h (ii) *THF* + *CDI* / 20°C, 3–4 h

Scheme 2

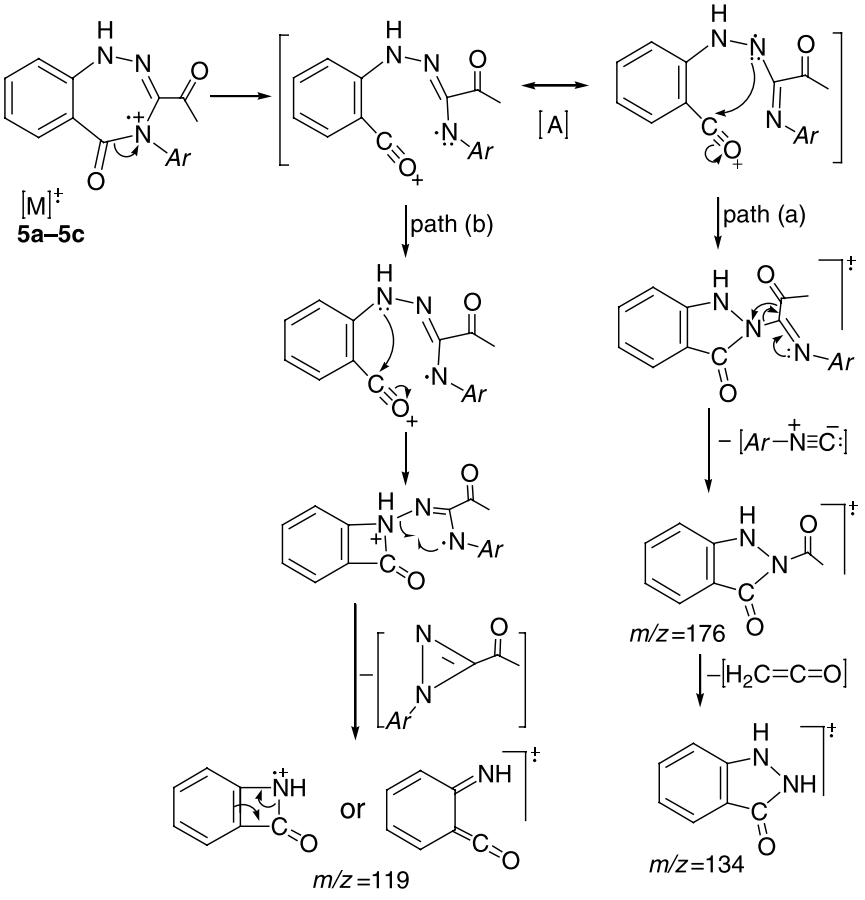
Results and Discussion

Synthesis

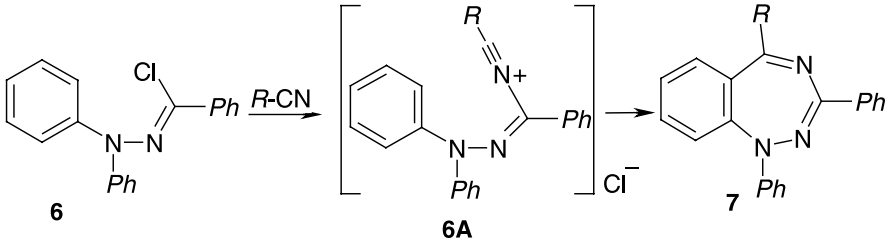
Benzeneamines (*Ar*NH_2), acting as nitrogen nucleophiles, add readily to nitrile imine (the reactive 1,3-dipolar species generated *in situ* from its hydrazonoyl chloride precursor **3** in presence of triethylamine) to produce the respective *N,N′*-diarylamidrazone adducts **4** (Scheme 2). This mode of nucleophilic addition reaction of various nucleophiles to 1,3-dipoles is well-documented, and several amidrazone adducts related to **4** have been obtained from the reaction of amines with hydrazonoyl chlorides (such as **3**) [4, 5]. The required hydrazonyl chloride **3** is prepared in this study *via* the *Japp-Klingemann* reaction [6–8] involving coupling of 2-carboxybenzenediazonium chloride (diazotized 2-aminobenzoic acid) with 3-chloro-2,4-pentanedione in aqueous-ethanolic sodium acetate. In a separate step, the acyclic adducts **4a**–**4c** in tetrahydrofuran in the presence of the coupling reagent *CDI* underwent cyclocondensation involving the activated carboxyl group and the hydrazone–NH terminus to furnish the corresponding dihydrobenzotriazepinones **5a**–**5c** (Scheme 2).

Spectroscopic Data

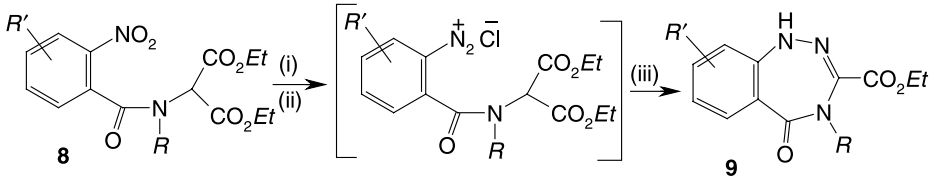
The IR, MS, and NMR spectral data and microanalyses of the new compounds **3**, **4a**–**4c**, **5a**–**5c** conform to the suggested structures, and are given in the Experimental part. Thus, their MS spectra display the correct molecular ions for which the measured high-resolution (HRMS) data are in good agreement with the calculated values. Under electron impact, the main fragmentation pattern for M^+ of compounds **5a**–**5c** involves initial ring opening of the dihydrotriazepinone system *via* heterolytic cleavage of the lactam bond to form the acyclic equivalent [**A**] (Scheme 3). Subsequently, expulsion of *Ar*NC from [**A**] produces the respective radical cation at $m/z = 176$, which then undergoes elimination of ketene to form the dihydroindazolone radical cation as the base peak at $m/z = 134$ (path (a)). Alternatively, the acyclic radical cation [**A**] undergoes extrusion of 3-acetyldiazirene with consequent production of the fragment ion at $m/z = 119$ (path (b)). ^{1}H and ^{13}C signal assignments follow from DEPT and 2D (COSY, HMQC and HMBC) experiments. Thus, long range correlation is observed between H-6 and each of C-9a and C-5 in HMBC experiments for compounds **5a**–**5c**. Likewise, H-8 is correlated with C-9a, while H-3′/H-5′ show correlation with C-1′.



Scheme 3



Scheme 4



(i) H_2 / catalyst (ii) $NaNO_2$ / HCl, 0°C (iii) NaOH (*JK* reaction)

Scheme 5

In this context, it is worth mentioning that the first examples of the 1,2,4-benzotriazepine system have been reported in 1974 by *Conde et al.* who synthesized several 5-substituted 1,3-diphenyl-1*H*-1,2,4-benzotriazepines **7** *via* intramolecular cyclization of the respective nitrilium salts **6A** (obtained from the reaction of benzhydrazidoyl chloride **6** with the appropriate nitrile in the presence of *Lewis* acid) (Scheme 4) [9]. Several 1,2,4-benzotriazepin-5-ones **9** have been later prepared from diethyl *N*-(2-nitrobenzoyl)aminomalonates **8** [10], *via* the *Japp-Klingemann* reaction [6–8] as depicted in Scheme 5.

In conclusion, the two-step reaction described in the present work (Scheme 2) provides an alternative and efficient route toward the synthesis of various substituted dihydro-1,2,4-benzotriazepin-5-ones **5** in good overall yield. This new versatile route utilizes readily available and inexpensive reactants (appropriately substituted anilines and *N*-(2-carboxyphenyl)hydrazonoyl chlorides), is conveniently conducted at or below room temp., and thus competes favorably with either of the literature methods cited above.

Experimental

2-Aminobenzoic acid was purchased from Merck, 4-methylaniline from Fluka, aniline, 4-chloroaniline, 3-chloro-2,4-pentanedine, and *CDI* from Acros. *THF* was dried over Na wire for 24 h before use. Melting points were measured on a Büchi 510 melting point apparatus. IR spectra were determined on KBr discs on a Nicolet Impact-400 FT-IR spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker-DPX 300 instrument with *TMS* as internal standard. Electron impact mass spectra (MS-EI) were obtained using a Varian MAT 212 spectrometer at 70 eV at an ion source temperature of 200°C. The new products were purified by preparative thick layer plates using silica gel (DFG_{254}, Merck) as the adsorbent. Microanalyses were performed at the Microanalytical Laboratory of the Hashemite University, Zarka-Jordan, and the results were found to be in good agreement (±0.4%) with the calculated values.

2-[N′-(1-Chloro-2-oxopropylidene)hydrazino]benzoic acid (**3**, $C_{10}H_9ClN_2O_3$)
2-Aminobenzoic acid (15.1 g, 0.11 mol) in 80 cm^3 cooled (0 to −5°C) 5*N* aqueous HCl was treated dropwise with a solution of 9.0 g aq $NaNO_2$ (0.13 mol) in 15 cm^3 H_2O under efficient stirring. The resulting solution was further stirred for 30 min at 0–4°C and then poured portionwise onto a vigorously stirred and cooled (−8 to −10°C, ice-salt bath) solution of 13.5 g 3-chloro-2,4-pentanedione (0.1 mol) and 16.4 g sodium acetate (0.2 mol) in 400 cm^3 ethanol. The reaction mixture was stirred for 30 min at 0–4°C, and then diluted with 400 cm^3 cold H_2O. The precipitated solid product 3 was collected, washed several times with cold H_2O, then with petroleum ether (bp 40–60°C), dried, and recrystallized from methanol. Yield 20.2 g (84%); mp 228–229°C; IR: $\bar{\nu} = 3240$, 3015, 1696, 1666, 1548, 1449, 1220 cm^{-1}; ^{1}H NMR (300 MHz, *DMSO*-d_6): $\delta = 2.49$ (s, COCH_3), 7.07 (dd, $J = 7.1$, 7.8 Hz, H-5), 7.57 (dd, $J = 8.2$, 7.1 Hz, H-4), 7.69 (d, $J = 8.2$ Hz, H-3), 7.91 (d, $J = 7.8$ Hz, H-6), 11.97 (s, C_2-NH), 13.80 (s, CO_2H) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): $\delta = 25.9$ (CO*C*H$_3$), 113.9 (C-1), 114.8 (C-3), 122.3 (C-5), 129.8 (Cl–*C*=N–), 131.9 (C-6), 135.4 (C-4), 144.3 (C-2), 170.0 (*C*O$_2$H), 188.4 (Me–*C*=O) ppm; MS-EI: m/z (%) = 240 (M^+, 76), 224 (17), 222 (49), 182 (19), 180 (56), 152 (11), 134 (62), 124 (28), 105 (13), 91 (50), 76 (14), 67 (37), 55 (100).

2-[N′-(1-(4-Methylphenylamino)-2-oxopropylidene)hydrazino]benzoic acid (**4a**, $C_{17}H_{17}N_3O_3$)
A homogeneous solution of 1.28 g *p*-methylaniline (12 mmol) in aqueous methanol and 6 cm^3 triethylamine was added dropwise to a stirred and cooled (0°C) solution of 2.41 g **3** (10 mmol) in 40 cm^3 *THF*. Additional triethylamine (4 cm^3) was then introduced dropwise into the reaction mixture which was stirred at 0°C for 1 h, then at room temp for 12–15 h. The organic solvents were removed *in vacuo*, and then the aqueous solution was acidified with glacial acetic acid. The resulting crude solid product was collected and recrystallized from $CHCl_3$/methanol (4/1, *v*/*v*) to give the yellow solid product **4a**. Yield 2.21 g (71%); mp 217–218°C; IR: $\bar{\nu} = 3186$, 2919, 1689, 1618, 1487, 1354 cm^{-1}; ^{1}H NMR (300 MHz, *DMSO*-d_6): $\delta = 2.13$ (s, $C_{4'}$–CH_3), 2.46 (s, COCH_3), 6.47 (d, $J = 8.1$ Hz, H-2′ + H-6′), 6.88 (dd, $J = 7.5$, 7.9 Hz, H-5), 6.92 (d, $J = 8.1$ Hz, H-3′ + H-5′), 7.55 (dd, $J = 8.1$, 7.5 Hz, H-4), 7.75–7.78 (m, H-3 + H-6), 8.09 (s, $C_{1'}$–N*H*), 10.80 (s, C_2-N*H*), 12.90 (br s, CO_2H) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): $\delta = 20.7$ ($C_{4'}$–*C*H$_3$), 25.0 (CO*C*H$_3$), 112.3 (C-1), 114.1 (C-3), 117.4 (C-2′ + C-6′), 119.9 (C-5), 129.3 (C-4′), 129.6 (C-3′ + C-5′), 131.6 (C-6), 135.1 (C-4), 137.8 (NH–*C*=N–), 138.1 (C-1′), 145.9 (C-2), 169.6 (*C*O$_2$H), 194.3(Me–*C*=O) ppm; MS-EI: m/z (%) = 311 (M^+, 20), 265 (45), 222 (30), 194 (14), 133 (30), 104 (100), 90 (68), 76 (15), 65 (17); HRMS: calcd for M^+ 311.1270, found 311.1282.

2-[N′-(1-(4-Chlorophenylamino)-2-oxopropylidene)hydrazino]benzoic acid (**4b**, $C_{16}H_{14}ClN_3O_3$)
This compound was prepared from 1.53 g *p*-chloroaniline (2 mmol) and 2.41 g **3** (10 mmol) by following the same procedure and experimental conditions described above for **4a**. The product was precipitated as an orange solid. Further purification was achieved by recrystallization from $CHCl_3$/methanol (4/1, *v*/*v*). Yield 2.06 g (62%); mp 235–236°C; IR: $\bar{\nu} = 3460$, 1651, 1487, 1356 cm^{-1}; ^{1}H NMR (300 MHz, *DMSO*-d_6): $\delta = 2.51$ (s, COCH_3), 6.55 (d, $J = 8.7$ Hz, H-2′ + H-6′), 6.91 (dd, $J = 7.4$, 7.5 Hz, H-5), 7.16 (d, $J = 8.7$ Hz, H-3′ + H-5′), 7.56 (dd, $J = 7.6$, 7.4 Hz, H-4), 7.76–7.80 (m, H-3 + H-6), 8.42 (s, $C_{1'}$–N*H*), 10.87 (s, C_2-N*H*), 13.08 (br, s, CO_2H) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): $\delta = 25.1$ (CO*C*H$_3$), 112.6 (C-1), 114.1 (C-3), 118.6 (C-2′ + C-6′), 120.3 (C-5), 124.1 (C-4′), 129.0 (C-3′ + C-5′), 131.7 (C-6), 135.1 (C-4), 137.4 (NH–*C*=N–), 139.6 (C-1′), 145.8 (C-2), 169.8 (*C*O$_2$H), 194.1 (Me–*C*=O) ppm; MS-EI: m/z (%) = 331 (M^+, 67), 152 (21), 134 (100), 119 (14), 91 (18), 65 (12); HRMS: calcd for M^+ 331.0723, found 331.0715.

2-[N′-(1-Phenylamino-2-oxopropylidene)hydrazino]benzoic acid (**4c**, $C_{16}H_{15}N_3O_3$)
This compound was prepared from 1.12 g aniline (12 mmol) and 2.41 g of **3** (10 mmol) by following the same procedure and experimental conditions described above for obtaining **4a**. The brown solid product that formed was recrystallized from $CHCl_3$/methanol (4/1, *v*/*v*). Yield 2.05 g (69%); mp 187–189°C; IR: $\bar{\nu} = 3460$, 1639, 1432, 1356 cm^{-1}; ^{1}H NMR (300 MHz, *DMSO*-d_6): $\delta = 2.46$ (s,

COCH_3), 6.56 (d, $J = 7.8$ Hz, H-2′ + H-6′), 6.75 (t, $J = 7.3$ Hz, H-4′), 6.89 (dd, $J = 7.5$, 7.5 Hz, H-5), 7.12 (dd, $J = 7.8$, 7.3 Hz, H-3′ + H-5′), 7.55 (dd, $J = 8.1$, 7.5 Hz, H-4), 7.77–7.80 (m, H-3 + H-6), 8.21 (s, $C_{1'}$–N*H*), 10.93 (s, C_2-N*H*), 13.20 (br, s, CO_2H) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): $\delta = 25.1$ (CO*C*H_3), 112.7 (C-1), 114.1 (C-3), 117.0 (C-2′ + C-6′), 120.1 (C-5), 120.6 (C-4′), 129.1 (C-3′ + C-5′), 131.7 (C-6), 135.0 (C-4), 137.8 (NH–*C*=N–), 140.6 (C-1′), 145.8 (C-2), 169.7 (*C*O_2H), 194.3 (Me–*C*=O) ppm; MS-EI: m/z (%) = 297 (M^+, 75), 152 (16), 134 (100), 119 (18), 104 (46), 91 (21), 76 (17), 65 (13); HRMS: calcd for M^+ 297.1113, found 297.1108.

3-Acetyl-4-(4-methylphenyl)-1,4-dihydro-1H-1,2,4-benzotriazepin-5-one (**5a**, $C_{17}H_{15}N_3O_2$)
CDI (0.41 g, 2.5 mmol) was added to a cooled (0°C) and stirred solution of 0.62 g **4a** (2 mmol) in 20 cm^3 dry *THF*, and the resulting mixture was further stirred at room temp for 2–3 h. The reaction mixture was then immediately treated with 20 cm^3 cold H_2O, most of the *THF* was then removed *in vacuo* and the aqueous layer was extracted with 2×20 cm^3 CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and the solvent was evaporated *in vacuo*. The residual yellow solid product was recrystallized from $CHCl_3$/petroleum ether (1/2, *v*/*v*). Yield 0.43 g (73%); mp 160–161°C; IR: $\bar{\nu} = 3316$, 1677, 1649, 1578, 1486, 1217 cm^{-1}; ^{1}H NMR (300 MHz, *DMSO*-d_6): $\delta = 2.15$ (s, COCH_3), 2.24 (s, $C_{4'}$–CH_3), 6.76 (d, $J = 7.7$ Hz, H-2′ + H-6′), 7.10–7.15 (m, H-7 + H-3′ + H-5′), 7.26 (d, $J = 7.7$ Hz, H-9), 7.63 (dd, $J = 7.7$, 7.4 Hz, H-8), 7.68 (d, $J = 7.7$ Hz, H-6), 11.21 (s, N_1-H) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): $\delta = 20.9$ ($C_{4'}$–*C*H_3), 30.9 (CO*C*H_3), 113.1 (C-9), 115.3 (C-5a), 121.1 (C-2′ + C-6′), 122.1 (C-7), 124.5 (C-6), 130.0 (C-3′ + C-5′), 133.9 (C-4′), 135.1 (C-8), 143.7 (C-1′), 148.6 (C-9a), 148.8 (C-3), 161.1 (C-5), 195.0 (Me–*C*=O) ppm; MS-EI: m/z (%) = 293 (M^+, 22), 176 (19), 134 (100), 119 (42), 90 (13); HRMS: calcd for M^+ 293.1164, found 293.1151.

3-Acetyl-4-(4-chlorophenyl)-1,4-dihydro-1H-1,2,4-benzotriazepin-5-one (**5b**, $C_{16}H_{12}Cl\ N_3O_2$)
This compound was prepared from 0.66 g **4b** (2 mmol) and 0.41 g *CDI* (2.5 mmol) by following the same procedure and experimental conditions described above for **5a**. The light-green product was recrystallized from $CHCl_3$/petroleum ether (1/2, *v*/*v*). Yield 0.52 g (83%); mp 140–141°C; IR: $\bar{\nu} = 3200$, 1684, 1641, 1485, 1407, 1357 cm^{-1}; ^{1}H NMR (300 MHz, *DMSO*-d_6): $\delta = 2.00$ (s, COCH_3), 6.89 (d, $J = 8.8$ Hz, H-2′ + H-6′), 7.13 (dd, $J = 7.7$, 7.7 Hz, H-7), 7.27 (d, $J = 8.2$ Hz, H-9), 7.36 (d, $J = 8.8$ Hz, H-3′ + H-5′), 7.63 (dd, $J = 8.2$, 7.7 Hz, H-8), 7.71 (d, $J = 7.7$ Hz, H-6), 11.20 (s, N_1-H) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): $\delta = 31.0$ (CO*C*H_3), 113.1 (C-9), 115.2 (C-5a), 122.3 (C-7), 123.1 (C-2′ + C-6′), 124.5 (C-6), 129.0 (C-4′), 129.5 (C-3′ + C-5′), 135.3 (C-8), 145.3 (C-1′), 148.8 (C-9a), 149.2 (C-3), 161.2 (C-5), 194.7 (Me–*C*=O) ppm; MS-EI: m/z (%) = 313 (M^+, 25), 235 (4), 176 (33), 134 (100), 119 (14), 91 (16); HRMS: calcd for M^+ 313.0618, found 313.0685.

3-Acetyl-4-phenyl-1,4-dihydro-1H-1,2,4-benzotriazepin-5-one (**5c**, $C_{16}H_{13}N_3O_2$)
This compound was prepared from 0.59 g **4c** (2 mmol) and 0.41 g *CDI* (2.5 mmol) by following the same procedure and experimental conditions described above for **5a**. The light-green product was recrystallized from $CHCl_3$/petroleum ether (1/2, *v*/*v*). Yield 0.22 g (40%); mp 170–172°C; IR: $\bar{\nu} = 3311$, 1693, 1620, 1487, 1355 cm^{-1}; ^{1}H NMR (300 MHz, *DMSO*-d_6): $\delta = 2.15$ (s, COCH_3), 6.76 (d, $J = 7.7$ Hz, H-2′ + H-6′), 7.07–7.16 (m, H-7 + H-4′), 7.26–7.34 (m, H-9 + H-3′ + H-5′), 7.63 (dd, $J = 8.0$, 7.4 Hz, H-8), 7.70 (d, $J = 7.8$ Hz, H-6), 11.20 (s, N_1-H) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): $\delta = 31.0$ (CO*C*H_3), 113.1 (C-9), 115.3 (C-5a), 121.2 (C-2′ + C-6′), 122.2 (C-7), 124.5 (C-6), 124.8 (C-4′), 129.5 (C-3′ + C-5′), 135.2 (C-8), 146.3 (C-1′), 148.7 (C-9a), 148.8 (C-3), 161.2 (C-5), 194.8 (Me–*C*=O) ppm; MS-EI: m/z (%) = 279 (M^+, 25), 176 (24), 134 (100), 119 (14), 104 (19), 91 (12); HRMS: calcd for M^+ 279.1008, found 279.1021.

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