JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

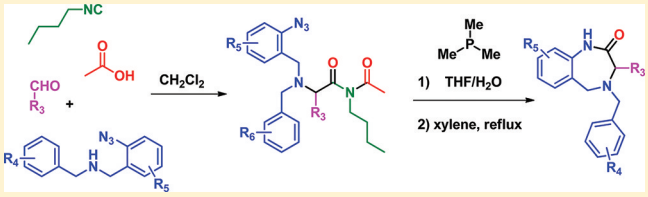
Exploiting the Acylating Nature of the Imide-Ugi Intermediate: A Straightforward Synthesis of Tetrahydro-1,4-benzodiazepin-2-ones

Riccardo Mossetti, Dèsirèe Saggiorato, and Gian Cesare Tron*

Dipartimento di Scienze Chimiche, Alimentari, Farmaceutiche e Farmacologiche, Università degli Studi del Piemonte Orientale "A. Avogadro", Via Bovio 6, 28100 Novara, Italy

Supporting Information

ABSTRACT: We describe a simple and novel protocol for the synthesis of tetrahydro-1,4-benzodiazepin-2-ones with three points of diversity, exploiting the acylating properties of the recently rediscovered Ugi-imide. The final compounds can be easily prepared in three synthetic steps using a multicomponent reaction, a Staudinger reduction, and an acylative protocol, with good to excellent yields for each synthetic step.



Benzodiazepines can be considered privileged structures in medicinal chemistry[1] because of their capability to bind specific domains of proteins. Over the last few decades, this scaffold has become an important structural unit in many pharmacologically relevant agents with biological activities not only restricted to CNS treatment.[2] For example, benzodiazepines endowed with antitumor[3] and anti-HIV[4] properties have been reported. Several synthetic approaches to benzodiazepines using the classical two-component chemistry have been described,[5] and several benzodiazepines (both 1,4- and 1,5-) have been synthesized using a multicomponent reaction, usually coupled with a postcondensation modification.[6] The search for different synthetic routes to benzodiazepines is a topic of continuous interest for both organic and medicinal chemists, as starting material availability and functional group tolerance can dictate which particular benzodiazepine-synthetic plan is best suited.

Among the different benzodiazepines, tetrahydro-1,4-benzodiazepin-2-ones[7] appear to be more difficult to prepare than the corresponding 1,4-benzodiazepine-2,5-ones, with only three synthetic strategies reported to date.[8] In 2000 and 2003, this scaffold was prepared by solid-phase synthesis using a multistep approach.[9] A drawback for this reaction is that the final product always contains a carboxamide group deriving from the release of the resin. In 2005, a patent was disclosed[10] in which this scaffold was prepared in six synthetic steps starting from 2-aminobenzylamine analogues, involving, among other things, an ozonolysis reaction and a Pd-catalyzed Suzuki reaction. Finally, a synthesis of 1,4-benzodiazepin-2-ones unsubstituted at the two nitrogen atoms by coupling the 2-nitrobenzyl bromide with a series of amino acids has been reported.[11] Because it is now well-understood that multicomponent reactions[12] offer a distinct advantage over the classical two-component chemistry favoring the preparation of libraries of compounds by simply varying each component and allowing the construction of molecules not easily accessible with the two component chemistry, herein we wish to report a novel synthesis of tetrahydro-1,4-benzodiazepin-2-ones by using a multicomponent reaction as a key step.

Very recently, we focused attention on the under-exploited imide-Ugi backbone (**5**), which can be easily prepared by a four-component reaction among a secondary amine (**1**), an aldehyde (**2**), a carboxylic acid (**3**), and an isocyanide (**4**) in dichloromethane in the presence of 4 Å molecular sieves.[13] We have also demonstrated that the presence of an imide compared with the unreactive bis-amide of the classical Ugi adduct expands the repertoire of the postcondensation reactions that can be used. For instance, because of their increased reactivity, imides can easily give an aza-Wittig reaction with the formation of quinazolinones (**6**) or 2,3-diaminoindoles (**7**) according to the position of the azide group. Furthermore, fully substituted pyrimidinones (**8**) were prepared by trapping, intramolecularly, the electrophilic carbonyl of the imide with an aliphatic amine (Figure 1).[13]

As it is well-known that imides have acylating properties,[14] we thought we might exploit this propensity by placing a nucleophilic group at the right position to be acylated generating the 1,4-benzodiazepine-2-one molecular scaffold (Figure 2).

Azido substituted dibenzylamines (**9**−**14**), which can be easily prepared by reductive amination between the amines and the corresponding azido benzaldehydes, were used as the amine component. In Figure 3, the secondary amines employed for this project are reported.

Using different aldehydes (both aliphatic and aromatic), the secondary amine described above, butyl isocyanide, and acetic acid in dichloromethane in the presence of 4 Å molecular sieves, the corresponding imides were obtained.[15] After column chromatography, the purified imides, which have not been characterized, were subjected to a Staudinger reduction[16] in order to reduce the aromatic azide group to aniline. The use of

Received: July 22, 2011
Published: November 9, 2011

dx.doi.org/10.1021/jo2015054 | J. Org. Chem. 2011, 76, 10258–10262

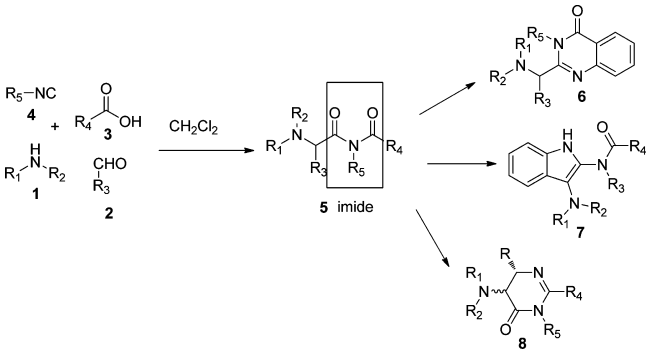


Figure 1. Different molecular scaffolds generated by postcondensation strategies of the imide-Ugi adduct.

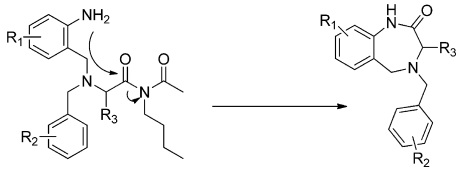


Figure 2. Proposed generation of tetrahydro-1,4-benzodiazepin-2-ones.

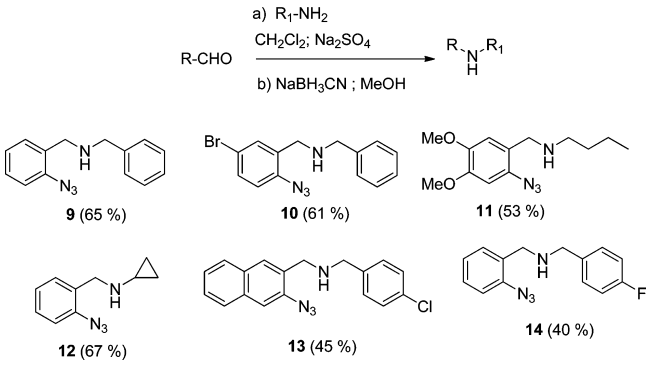


Figure 3. Secondary amine building blocks.

trimethyl phosphine was compulsory for the success of the reduction step, as using triphenyl phosphine or even tributylphosphine, the corresponding iminophosphorane was very stable and reluctant to react with water even at reflux conditions. After the Staudinger reduction, the solvent was evaporated, and the residue was dissolved in xylene and heated at reflux, bringing the formation of the desired 1,4-benzodiazepin-2-ones. The use of butyl isocyanide (**15**) and acetic acid (**16**), which are lost during the formation of the benzodiazepine scaffold, was the best compromise between reactivity and atom economy. (Scheme 1)

In Figure 4 are represented the tetrahydro-1,4-benzodiazepine-2-ones (**17**–**29**) prepared with this procedure with yields ranging from 14 to 46%. Yields are referred over three synthetic steps (a multicomponent reaction, a Staudinger reaction, and an acylative protocol), indicating an average yield of 71–82% for each synthetic step.

Aliphatic as well as aromatic aldehydes were well-tolerated, and the presence of an electron-withdrawing group in the same aromatic ring of the amine was not detrimental for the ring closure. When aromatic aldehydes were used, the corresponding benzodiazepinones precipitate, and the final compounds can be easily obtained by filtration.

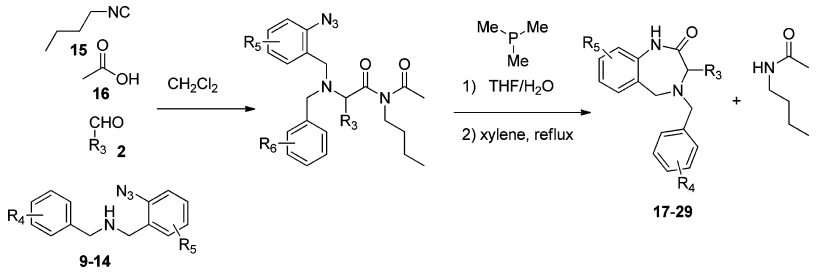
In conclusion, we disclosed a new postcondensation transformation of the so-called imide Ugi-adduct exploiting the strong acylating properties of the imide group, which led to the facile and rapid synthesis of 1,4-benzodiazepin-2-ones with three points of diversity. Compared with the synthesis of tetrahydro-1,4-benzodiazepin-2-ones reported to date, this procedure does not require the use of advanced intermediates and transition metals, but only the use of cheap commercially available aldehydes, butyl isocyanide, and acetic acid and easily accessible secondary amines with an azide group. The biological investigation of the synthesized compounds is under evaluation and the results will be reported in due course.

EXPERIMENTAL SECTION

Chemistry. Commercially available reagents and solvents were used without further purification. Dichloromethane was purified by distillation on P_2O_5 and stored on activated molecular sieves (4 Å). When needed, the reactions were performed in flame- or oven-dried glassware under a positive pressure of dry N_2 or in a Schlenk tube. Melting points were determined in open glass capillary and are uncorrected. Chemical shifts are reported in parts per million (ppm). Column chromatography was performed on silica gel 70–230 mesh ASTM or silica gel 230–400 ASTM. Thin layer chromatography (TLC) was carried out on 5 × 20 cm plates with a layer thickness of 0.25 mm (silica gel 60 F_{254}). When necessary, they were developed with $KMnO_4$ or Dragendorff reagent. The purity of the target compounds (>95%) was analyzed via elemental analysis and was within ±0.4% of the calculated value.

General Procedure for the Preparation of the Amines 9–14. To a solution of the corresponding azidoaldehyde (1 equiv) and the corresponding amine (1 equiv) in dry dichloromethane, sodium sulfate (4 equiv) was added. The reaction was vigorously stirred at room temperature for 3 h. Sodium sulfate was filtered off, and the filtrate was evaporated. The crude residue was dissolved in MeOH and acetic acid (5 equiv) and cooled at 0 °C, and $NaBH_3CN$ (1 equiv) was added portionwise. The reaction was then stirred at room temperature for 2 h. The reaction was worked up by addition of 2 N HCl and extracted with EtOAc (× 2). The aqueous phase was basified with 6 N NaOH (pH > 12) and extracted with EtOAc (× 3). The collected organic layers were washed with brine (× 1). Drying over sodium

Scheme 1. Synthetic Scheme for the Generation of the Tetrahydro-1,4-benzodiazepin-2-ones



dx.doi.org/10.1021/jo2015054 | J. Org. Chem. 2011, 76, 10258–10262

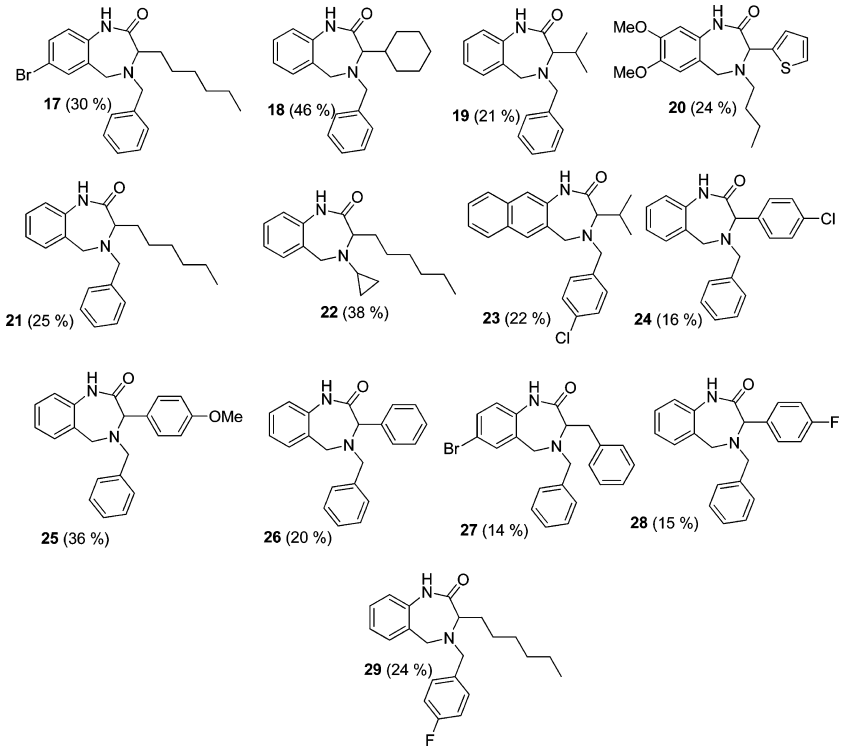


Figure 4. Tetrahydro-1,4-benzodiazepin-2-ones synthesized. Yields are referred over three steps.

sulfate and evaporation of the solvent gave the corresponding amine as a yellow oil.

Caution: Trimethylphosphine has pyrophoric tendencies and is very volatile (bp 38−39 °C).

*N-(2-Azidobenzyl)-1-phenylmethanamine (**9**):* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50−7.28 (m, 8H), 7.23−7.10 (m, 2H), 3.84 (s, 2H), 3.82 (s, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 140.8, 138.7, 132.0, 130.9, 128.9, 128.7, 127.5, 125.3, 118.7, 53.7, 49.4; ν_{max}(neat)/cm^{-1} 3026, 2119, 1487, 1451, 1281; MS (ESI) *m*/*z* 239 (M + H)$^+$. Yellow oil.

*N-(2-Azido-5-bromobenzyl)-1-phenylmethanamine (**10**):* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, *J* = 2.3 Hz, 1H), 7.41 (dd, *J* = 8.4 Hz, 2.3 Hz, 1H), 7.38−7.25 (m, 6H), 7.00 (d, *J* = 8.4 Hz), 3.79 (s, 2H), 3.72 (s, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 140.5, 137.8, 134.2, 133.5, 131.6, 129.0, 128.7, 127.6, 120.1, 118.3 53.7, 48.8; ν_{max}(neat)/cm^{-1} 3110, 2121, 1480, 1275; MS (ESI) *m*/*z* 317/319 (M + H)$^+$. Yellow oil.

*N-(2-Azido-4,5-dimethoxybenzyl)butan-1-amine (**11**):* ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.80 (s, 1H), 6.58 (s, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 2.54 (t, *J* = 6.9 Hz, 2H), 1.73 (broad s, 1H), 1.44 (quint, *J* = 7.1 Hz, 2H), 1.30 (sext, *J* = 7.1 Hz, 2H), 0.85 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 149.3, 146.7, 130.2, 123.9, 113.8, 102.3, 56.5, 56.4, 49.4 (2C), 32.4, 20.8, 14.3; ν_{max}(neat)/cm^{-1} 3361, 2108, 1736, 1259; MS (ESI) *m*/*z* 265 (M + H)$^+$. Yellow oil.

*N-(2-Azidobenzyl)cyclopropanamine (**12**):* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27−7.13 (m, 2H), 7.08−6.93 (m, 2H), 3.71 (s, 2H), 2.25 (s, 1H), 2.06−1.94 (m, 1H), 0.42−0.29 (m, 4H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 138.5, 132.2, 130.9, 128.7, 125.0, 118.4, 49.7, 30.2, 6.9, 6.8; ν_{max}(neat)/cm^{-1} 3108, 2106, 1275; MS (ESI) *m*/*z* 189 (M + H)$^+$. Yellow oil.

*1-(3-Azidonaphthalen-2-yl)-N-(4-chlorobenzyl)methanamine (**13**):* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 9.1 Hz, 1H), 7.73 (d, *J* = 4.4 Hz, 2H), 7.54−7.40 (m, 3H), 7.36−7.24 (m, 5H), 3.88 (s, 2H), 3.78 (s, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 139.2, 137.6, 133.8, 131.5, 131.0, 130.1, 129.8, 129.1, 128.2, 127.2, 126.9, 126.2, 116.1, 52.8, 49.7; ν_{max}(neat)/cm^{-1} 3106, 2120, 1264; MS (ESI) *m*/*z* 323/325 (M + H)$^+$. Yellow oil.

*N-(2-Azidobenzyl)-1-(4-fluorophenyl)methanamine (**14**):* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.25 (m, 4H), 7.16−7.10 (m, 2H), 7.02 (br t, 2H), 3.74 (br s, 4H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 162,0 (d, *J* = 242 Hz), 138.3, 136.0 (d, *J* = 2 Hz), 131.4, 129.8 (d, *J* = 8.0 Hz), 128.6, 124.8, 115.1 (d, *J* = 21.18 Hz), 52.4, 48.9; ν_{max}(neat)/cm^{-1} 3100, 2100, 1310; MS (ESI) *m*/*z* 216 (M + H)$^+$. Yellow oil.

General Procedure for the Preparation of the Tetrahydro-1,4-benzodiazepin-2-ones (17−29). Aldehyde (1 equiv), acetic acid (1 equiv), and butyl isocyanide (1 equiv) were added sequentially to a solution of amine (1 equiv) in dry dichloromethane with molecular sieves 4 Å. The reaction was stirred at room temperature for 2 h (when aromatic aldehyde was used, the reaction was stirred at 40 °C for 3 days). The solvent was evaporated, and the imide was purified by column chromatography (the unreacted aromatic aldehydes were eliminated via Bertagnini reaction). The imide was then dissolved with THF/water 1:1 and cooled at 0 °C. Trimethylphosphine (1.7 equiv) (1.0 M solution in toluene) was added, and the reaction was stirred at room temperature for 30 min. The reaction was diluted with EtOAc and washed with water (× 1). After evaporation of the organic solvent, the crude residue was dissolved in xylene, and the reaction was heated at reflux for 3−4 h. Evaporation of the solvent, followed by column chromatography, yielded the desired tetrahydro-1,4-benzodiazepin-2-one.

*4-Benzyl-7-bromo-3-hexyl-4,5-dihydro-1H-benzo[e][1,4]-diazepin-2(3H)-one (**17**):* ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (broad s, 1H), 7.41−7.10 (m, 7H), 6.86 (d, *J* = 8.3 Hz, 1H), 3.88 (d, *J* = 15.4 Hz, 1H), 3.81 (d, *J* = 13.5 Hz, 1H), 3.69 (d, *J* = 15.4 Hz, 1H), 3.59 (d, *J* = 13.5 Hz, 1H), 3.53 (t, *J* = 7.7 Hz, 1H), 1.97−1.81 (m, 1H), 1.77−1.58 (m, 1H), 1.53−1.12 (m, 8H), 0.87 (t, *J* = 6.3 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 172.0, 136.0, 133.7, 130.6, 129.0, 128.9, 126.6, 126.5, 125.1, 119.4, 114.6, 63.0, 54.0, 50.3, 29.6, 28.2, 26.7, 24.1, 20.3, 11.8; ν_{max}(KBr)/cm^{-1} 1653, 1490, 1223, 958; MS (ESI) *m*/*z* 415/417 (M + H)$^+$. White solid: mp 86.3−86.6 °C. Anal. Calcd for $C_{22}H_{27}BrN_2O$: C, 63.61; H, 6.55; N, 6.74. Found C, 64.34; H, 6.20; N, 6.32.

*4-Benzyl-3-cyclohexyl-4,5-dihydro-1H-benzo[e][1,4]diazepin-2(3H)-one (**18**):* ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.75 (broad s, 1H), 7.44−7.21 (m, 6H), 7.16−6.97 (m, 3H), 3.98 (d, *J* = 13.1 Hz, 1H), 3.71 (s, 2H), 3.66 (d, *J* = 13.1 Hz, 1H), 3.27 (d, *J* = 10.4 Hz, 1H), 2.12 (d, *J* = 12.9 Hz, 1H), 1.80−1.37 (m, 5H), 1.20−0.78 (m, 5H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 174.2, 139.3, 138.0, 130.4, 130.3, 129.2,

dx.doi.org/10.1021/jo2015054 | *J. Org. Chem.* 2011, 76, 10258−10262

128.9, 128.8, 127.6, 125.1, 120.6, 71.8, 59.8, 54.6, 37.8, 30.9, 30.4, 27.0, 26.3 (2C); ν_{max}(KBr)/cm^{-1} 1659, 1589, 1494, 760; MS (ESI) *m*/*z* 335 (M + H)$^+$. White solid: mp 182.5−182.8 °C. Anal. Calcd for $C_{22}H_{26}N_2O$: C, 79.00; H, 7.84; N, 8.38. Found C, 79.34; H,8.20; N, 8.00.

4-Benzyl-3-isopropyl-4,5-dihydro-1H-benzo[e][1,4]diazepin-2(3H)-one (**19**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (broad s, 1H), 7.45−7.21 (m, 6H), 7.16−7.04 (m, 2H), 7.01 (d, *J* = 8.0 Hz, 1H), 3.99 (d, *J* = 13.2 Hz, 1H), 3.77−3.61 (m, 3H), 3.13 (d, *J* = 10.4 Hz, 1H), 1.80−1.64 (m, 1H), 0.98 (d, *J* = 6.0 Hz, 3H), 0.89 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 174.2, 139.3, 138.0, 130.5, 130.4, 129.3, 129.0, 128.8, 127.6, 125.2, 120.7, 73.2, 59.9, 54.8, 28.6, 20.4, 20.1; ν_{max}(KBr)/cm^{-1} 1673, 1489, 1266, 761; MS (ESI) *m*/*z* 295 (M + H)$^+$. White solid: mp 120.1−120.5 °C. Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found C, 77.50; H,7.40; N, 9.50

4-Butyl-7,8-dimethoxy-3-(thiophen-2-yl)-4,5-dihydro-1H-benzo-[e][1,4]diazepin-2(3H)-one (**20**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.78 (broad s, 1H), 7.20 (d, *J* = 5.0 Hz, 1H), 6.98−6.83 (m, 2H), 6.64 (s, 1H), 6.54 (s, 1H), 4.58 (s, 1H), 4.01 (d, *J* = 14.6 Hz, 1H), 3.86 (s, 3H), 3.81 (s, 3H), 3.72 (d, *J* = 14.6 Hz, 1H), 2.52 (t, *J* = 6.9 Hz, 2H), 1.78−1.19 (m, 4H), 0.87 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 173.1, 149.5, 146.7, 143.7, 130.6, 126.7, 126.5, 126.2, 121.2, 113.5, 105.3, 67.1, 56.8, 56.6, 53.1, 52.6, 30.4, 20.8, 14.5; ν_{max}(KBr)/cm^{-1} 1662, 1512, 1251, 1133, 704; MS (ESI) *m*/*z* 361 (M + H)$^+$. Brownish solid: mp 164.0−164.4 °C. Anal. Calcd for $C_{19}H_{24}N_2O_3S$: C, 63.31; H, 6.71; N, 7.77. Found C, 63.60; H, 6.92; N, 8.12.

4-Benzyl-3-hexyl-4,5-dihydro-1H-benzo[e][1,4]diazepin-2(3H)-one (**21**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (broad s, 1H), 7.43−7.21 (m, 6H), 7.06 (d, *J* = 5.2 Hz, 2H), 6.98 (d, *J* = 8.0 Hz, 1H), 3.88 (d, *J* = 14.8 Hz, 1H), 3.84 (d, *J* = 13.5 Hz, 1H), 3.73 (d, *J* = 14.8 Hz, 1H), 3.60 (d, *J* = 13.5 Hz, 1H), 3.54 (t, *J* = 7.1 Hz, 1H), 2.0−1.84 (m, 1H), 1.81−1.64 (m, 1H), 1.53−1.14 (m, 8H), 0.87 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (300 MHz, CDCl3) δ 176.2, 139.2, 137.4, 131.0, 130.7, 129.3, 128.8 (2C), 127.6, 124.7, 120.5, 65.5, 56.9, 53.5, 32.2, 30.9, 29.5, 26.7, 23.0, 14.5; ν_{max}(KBr)/cm^{-1} 1672, 1589, 1492, 1290, 769; MS (ESI) *m*/*z* 337 (M + H)$^+$. White solid: mp 83.3−83.8 °C. Anal. Calcd for $C_{22}H_{28}N_2O$: C, 78.53; H, 8.39; N, 8.33. Found C, 78.05; H,8.12; N, 8.78.

4-Cyclopropyl-3-hexyl-4,5-dihydro-1H-benzo[e][1,4]diazepin-2(3H)-one (**22**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.86 (br s, 1H), 7.27−7.16 (m, 2H), 7.09−6.97 (m, 2H), 4.01 (d, *J* = 14.9 Hz, 1H), 3.87 (d, *J* = 14.9 Hz, 1H), 3.59 (t, *J* = 7.7 Hz, 1H), 2.08−1.99 (m, 1H), 1.79 (quint, *J* = 7.1 Hz, 1H), 1.65−1.50 (m, 1H), 1.48−0.98 (m, 8H), 0.84 (t, *J* = 6.6 Hz, 3H), 0.57−0.36 (m, 4H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 176.6, 137.5, 130.5, 129.8, 128.7, 124.6, 120.5, 67.1, 54.2, 35.3, 32.1, 31.3, 29.5, 26.9, 23.0, 14.5, 8.2, 7.3; ν_{max}(KBr)/cm^{-1} 1653, 1592, 1440, 1048, 884; MS (ESI) *m*/*z* 287 (M + H)$^+$. White solid: mp 87.1−87.6 °C. Anal. Calcd for $C_{18}H_{26}N_2O$: C, 75.48; H, 9.15; N, 9.78. Found C, 75.78; H, 9.43; N, 9.46.

4-(4-Chlorobenzyl)-3-isopropyl-4,5-dihydro-1H-naphtho[2,3-e]-[1,4]diazepin-2(3H)-one (**23**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (broad s, 1H), 7.76 (d, *J* = 9.1 Hz, 2H), 7.64 (s, 1H), 7.52−7.22 (m, 7H), 4.01 (d, *J* = 13.2 Hz, 1H), 3.79 (d, *J* = 12.1 Hz, 1H), 3.65 (d, *J* = 12.1 Hz, 1H), 3.58 (d, *J* = 13.2 Hz, 1H), 1.80−1.51 (m, 1H), 0.89 (d, *J* = 6.6 Hz, 3H), 0.82 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 172.6, 137.8, 136.5, 134.0, 133.2, 131.8, 130.8, 130.3, 129.8, 129.1, 128.1, 127.6, 127.4, 126.2, 117.6, 72.2, 59.5, 56.1, 28.4, 20.4, 19.9; ν_{max}(KBr)/cm^{-1} 1670, 1490, 1258, 1074, 750; MS (ESI) *m*/*z* 379/381 (M + H)$^+$. White solid: mp 194.2−194.3 °C. Anal. Calcd for $C_{23}H_{23}ClN_2O$: C, 72.91; H, 6.12; N, 7.39. Found C, 73.05; H, 6.30; N, 7.12.

4-Benzyl-3-(4-chlorophenyl)-4,5-dihydro-1H-benzo[e][1,4]-diazepin-2(3H)-one (**24**): ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.00 (broad s, 1H), 7.42 (d, *J* = 8.5 Hz, 2H), 7.38−7.25 (m, 8H), 7.13 (d, *J* = 8.5 Hz, 2H), 7.05 (d, *J* = 7.7 Hz, 1H), 4.19 (s, 1H), 3.91 (d, *J* = 14.3 Hz, 1H), 3.55 (d, *J* = 14.3 Hz, 1H), 3.47 (d, *J* = 4.1 Hz, 1H); ^{13}C NMR (300 MHz, DMSO-d_6) δ 168.3, 136.6 (2C), 136.0, 130.1, 128.9, 128.5, 126.9 (2C), 126.7, 126.0, 125.5, 125.4, 122.7, 119.1, 67.6, 54.2, 49.6; ν_{max}(KBr)/cm^{-1} 1670, 1492, 1263, 743; MS (ESI) *m*/*z* 363/365 (M + H)$^+$. White solid: mp 242.5−242.7 °C. Anal. Calcd for $C_{22}H_{19}ClN_2O$: C, 72.82; H, 5.28; N, 7.72. Found C, 72.65; H, 5.26; N, 7.60.

4-Benzyl-3-(4-methoxyphenyl)-4,5-dihydro-1H-benzo[e][1,4]-diazepin-2(3H)-one (**25**): ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.08 (s, 1H), 7.41−7.23 (m, 8H), 7.18−7.04 (m, 3H), 6.87 (d, *J* = 8.8 Hz, 2H), 4.05 (s, 1H), 3.86 (d, *J* = 14.3 Hz, 1H), 3.72 (s, 3H), 3.46 (t, *J* = 14.3 Hz, 2H), 3.30 (d, *J* = 14.3 Hz, 1H); ^{13}C NMR (300 MHz, DMSO-d_6) δ 169.0, 156.9, 136.8, 136.6, 128.7, 128.5, 128.3, 126.8 (2C), 126.6, 125.4, 125.3, 122.4, 118.9, 111.5, 67.7, 53.7, 53.2, 49.3; ν_{max}(KBr)/cm^{-1} 1672, 1516, 1492, 1249, 744; MS (ESI) *m*/*z* 359 (M + H)$^+$. White solid: mp 219−219.3 °C. Anal. Calcd for $C_{23}H_{22}N_2O_2$: C, 77.07; H, 6.19; N, 7.82. Found C, 77.00; H, 6.40; N, 7.69.

4-Benzyl-3-phenyl-4,5-dihydro-1H-benzo[e][1,4]diazepin-2(3H)-one (**26**): ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.12 (broad s, 1H), 7.48−7.19 (m, 11H), 7.17−7.03 (m, 3H), 4.13 (s, 1H), 3.88 (d, *J* = 14.3 Hz, 1H), 3.57−3.27 (m, 3H); ^{13}C NMR (300 MHz, DMSO-d_6) δ 169.3, 137.2, 136.9, 136.4, 128.1, 126.8, 126.6, 126.5 (2C), 125.9, 125.3 (2C), 122.0, 118.7, 69.3, 55.3, 50.3; ν_{max}(KBr)/cm^{-1} 1670, 1492, 1340, 1269, 746; MS (ESI) *m*/*z* 329 (M + H)$^+$. White solid: mp 270.4−270.8 °C. Anal. Calcd for $C_{22}H_{20}N_2O$: C, 80.46; H, 6.14; N, 8.53. Found C, 80.40; H, 6.15; N, 8.32.

3,4-Dibenzyl-7-bromo-4,5-dihydro-1H-benzo[e][1,4]diazepin-2(3H)-one (**27**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50−7.08 (m, 13H), 6.88 (d, *J* = 8.5 Hz, 1H), 4.04−3.79 (m, 3H), 3.66 (d, *J* = 10.4 Hz, 1H), 3.61 (d, *J* = 8.8 Hz, 1H), 3.32 (dd, *J* = 14.0 Hz, 6.9 Hz, 1H), 2.96 (dd, *J* = 14.0 Hz, 7.4 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 172.0, 136.2, 135.8, 133.9, 130.6, 129.2, 128.9, 127.1, 126.5, 126.2, 126.0, 125.1, 124.1, 119.7, 114.9, 64.8, 54.4, 50.7, 34.6; ν_{max}(KBr)/cm^{-1} 1643, 1480, 1399, 867; MS (ESI) *m*/*z* 421/423 (M + H)$^+$. White solid: mp 128.3−128.7 °C. Anal. Calcd for $C_{23}H_{21}BrN_2O$: C, 65.57; H, 5.02; N, 6.65. Found C, 65.40; H, 4.82; N, 6.87.

4-Benzyl-3-(4-fluorophenyl)-4,5-dihydro-1H-benzo[e][1,4]-diazepin-2(3H)-one (**28**): ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.43−7.30 (m, 6H), 7.29−7.21 (m, 2H), 7.13−6.97 (m, 5H), 4.34 (s, 1H), 3.95 (d, *J* = 14.3 Hz, 1H), 3.64 (d, *J* = 14.3 Hz, 1H), 3.59 (d, *J* = 2.8 Hz, 2H); ^{13}C NMR (300 MHz, DMSO-d_6) δ 171.2, 160.0 (d, *J* = 242 Hz), 139.1, 138.8, 135.6, 130.7 (d, *J* = 7.4 Hz), 130.5, 129.1 (2C), 128.8 (2C), 128.5, 127.6, 124.5, 121.1, 114.9 (d, *J* = 21,2 Hz), 70.7, 57.5, 52.5; ν_{max}(KBr)/cm^{-1} 1633, 1530, 1290, 980, 867; MS (ESI) *m*/*z* 347 (M + H)$^+$. White solid: mp 250−251 °C. Anal. Calcd for $C_{22}H_{19}FN_2O$: C, 76.28; H, 5.53; N, 8.09. Found C, 76.50; H, 5.82; N, 7.80.

4-(4-Fluorobenzyl)-3-hexyl-4,5-dihydro-1H-benzo[e][1,4]-diazepin-2(3H)-one (**29**): ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.90 (br s, 1H), 7.34−7.20 (m, 3H), 7.10−6.96 (m, 5H), 3.89 (d, *J* = 15.1 Hz, 1H), 3.78 (t, *J* = 13.5 Hz, 1H), 3.70 (d, *J* = 15.1 Hz, 1H), 3.63−3.47 (m, 2H), 2.01−1.83 (m, 1H), 1.78−1.62 (m, 1H), 1.52−1.18 (m, 8H), 0.87 (t, *J* = 6.6 Hz, 1H); ^{13}C NMR (300 MHz, DMSO-d_6) δ 175.7, 162.1 (d, *J* = 243,3 Hz), 137.1, 134.5, 130.3 (d, *J* = 11.4 Hz), 128.7, 128.5, 124.3, 120.3, 115.2 (d, *J* = 21,2 Hz), 65.3, 55.9, 53.0, 31.9, 30.7, 29.1, 26.4, 22.7, 14.2; ν_{max}(KBr)/cm^{-1} 1630, 1450, 1250, 870; MS (ESI) *m*/*z* 355 (M + H)$^+$. Amorphous solid. Anal. Calcd for $C_{22}H_{27}FN_2O$: C, 74.55; H, 7.68; N, 7.90. Found C, 74.50; H, 7.72; N, 8.05.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Characterization data and copies of ^{1}H and ^{13}C NMR spectra for all compounds synthesized. This information is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Tel.: +39-0321-375857. Fax: +39-0321-375821. E-mail: tron@pharm.unipmn.it.

■ ACKNOWLEDGMENTS

Financial support from Università del Piemonte Orientale, Italy is gratefully acknowledged.

■ REFERENCES

(1) (a) Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S.; Chang, R. S. L.; Lotti, V. J.; Chen, T. B.; Kling, P. J.; Kinkel, K. A.; Springer, J. P.; Hirshfield, J. *J. Med. Chem.* **1988**, *31*, 2235−2246. (b) Costantino, L.; Barlocco, D. *Curr. Med. Chem.* **2006**, *13*, 65−85.

(2) Hamor, T. A.; Martin, I. L. *Prog. Med. Chem.* **1983**, *20*, 157−223.

(3) (a) Nawrocka, W.; Sztuba, B.; Opolski, A.; Wietrzk, J.; Kowalska, M. W.; Tadeusz, G. *Arch. Pharm.* **2001**, *334*, 3−10. (b) Forso, S. *Mini-Rev. Med. Chem.* **2010**, *7*, 68−74.

(4) Breslin, H. J.; Kukla, M. J.; Ludovici, D. W.; Mohrbacher, R.; Ho, W.; Miranda, M.; Rodgers, J. D.; Hitchens, T. K.; Leo, G.; Gauthier, D. A.; Ho, C. Y.; Scott, M. K.; De Clercq, E.; Pauwels, R.; Andries, K.; Janssen, M. A. C.; Janssen, P. A. *J. Med. Chem.* **1995**, *38*, 771−793.

(5) (a) Archer, G. A.; Sternbach, L. *Chem. Rev.* **1968**, *68*, 747−784.

(6) (a) Sanudo, M.; Garcia-Valverde, M.; Marcaccini, S.; Delgado, J. J.; Rojo, J.; Torroba, T. *J. Org. Chem.* **2009**, *74*, 2189−2192. (b) Tempest, P.; Pettus, L.; Gore, V.; Hulme, C. *Tetrahedron Lett.* **2003**, *44*, 1947−1959. (c) Alizadeh, A.; Zohreh, N.; Zhu, L. G. *Tetrahedron* **2008**, *65*, 2684−2688. (d) Murai, K.; Nakatani, R.; Kita, Y.; Fujioka, H. *Tetrahedron* **2008**, *64*, 11034−11040. (e) Marcaccini, S.; Miliciani, M.; Pepino, R. *Tetrahedron Lett.* **2005**, *46*, 711−713. (f) Lecinska, P.; Corres, N.; Moreno, D.; Garcia-Valverde, M.; Marcaccini, S.; Torroba, T. *Tetrahedron* **2010**, *66*, 6783−6788. (g) Kalinsky, C.; Umkehrer, M.; Ross, G.; Kilb, J.; Burdack, C.; Hiller, W. *Tetrahedron Lett.* **2006**, *47*, 3423−3426. (h) Zohreh, N.; Alizadeh, A.; Bijanzdeh, H. R.; Zhu, L. G. *J. Comb. Chem.* **2010**, *12*, 497−502. (i) Shaabani, A.; Maleki, A.; Hajishaabanha, F.; Mofakham, H.; Seyyedhamzeh, M.; Mahyari, M.; Ng, S. W. *J. Comb. Chem.* **2010**, *12*, 186−190. (j) Cuny, G.; Nois-Choussy, M.; Zhu, J. *J. Am. Chem. Soc.* **2004**, *126*, 14475−14484. (k) Keating, T. A.; Armstrong, R. W. *J. Am. Chem. Soc.* **1996**, *118*, 2574−2583.

(7) Spencer, J.; Rathnam, R. P.; Chowdhry, B. Z. *Future Med. Chem.* **2010**, *2*, 1441−1449.

(8) For other syntheses of benzodiazepine-ones using different approaches see: (a) Liu, A.; Zhou, H.; Su, G.; Zhang, W.; Yan, B. *J. Comb. Chem.* **2009**, *11*, 1083−1093. (b) Zhou, H.; Zhang, W.; Yan, B. J. *J. Comb. Chem.* **2010**, *12*, 206−214. (c) Hulme, C.; Chappeta, S.; Dietrich, J. *Tetrahedron Lett.* **2009**, *50*, 4054−4057. (d) Xu, Z.; Dietrich, J.; Shaw, A. Y.; Hulme, C. *Tetrahedron Lett.* **2010**, *51*, 4566−4569.

(9) (a) Zhang, J.; Goodloe, W. P.; Lou, B.; Saneii, H. *Mol. Diversity* **2000**, *5*, 127−130. (b) Wu, Z.; Ercole, F.; FitzGerald, M.; Perera, S.; Riley, P.; Campbell, R.; Pham, Y.; Rea, P.; Sandanayake, S.; Mathieu, M. N.; Bray, A. M.; Ede, N. J. *J. Comb. Chem.* **2003**, *5*, 166−171. (c) Hone, N. D.; Wilson, W.; Reader, J. C. *Tetrahedron Lett.* **2003**, *44*, 8493−8495.

(10) Petasis, N. A.; Yao, X.; Raber, J. C. US Patent 6927294 (2005)

(11) Mishra, J. K.; Panda, G. *Synthesis* **2005**, 1881−1887.

(12) (a) *Multicomponent Reactions*; Zhu, J., Bienaymè, H., Eds.; Wiley-VCH: Weinheim, Germany, 2005 and references therein. (b) *Synthesis of Heterocycles via Multicomponent Reactions I and II*; Orru, R. V. A., Ruijeter, E., Eds.; Springer GmbH, Berlin, Germany, 2010 and references therein.

(13) Mossetti, R.; Pirali, T.; Saggiorato, D.; Tron, G. C. *Chem. Commun.* **2011**, *47*, 6966−6968.

(14) Ugi, I.; Steinbrückner, C. *Chem. Ber.* **1961**, *94*, 2802−2814.

(15) With the aliphatic aldeydes, the imides were prepared after 1−2 h, whereas aromatic aldehydes required an increased time of 1−3 days.

(16) Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635−646.