HETEROCYCLES, Vol. 87, No. 8, 2013, pp. 1765 - 1773. © 2013 The Japan Institute of Heterocyclic Chemistry
Received, 31st May, 2013, Accepted, 19th June, 2013, Published online, 27th June, 2013
DOI: 10.3987/COM-13-12752

THREE-STEP SYNTHESIS OF TRIAZOLOBENZODIAZEPINONES VIA SONOGASHIRA/HUISGEN PROTOCOL

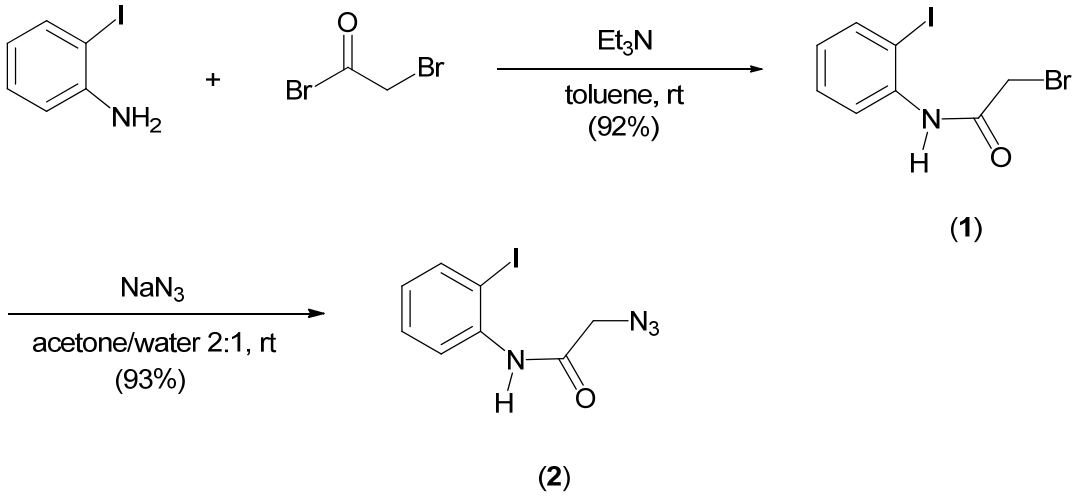
Giorgio Molteni*

Università degli Studi di Milano, Dipartimento di Chimica, via Golgi 19, 20133 Milano, Italy

Abstract – The sequential Sonogashira coupling/intramolecular azide cycloaddition (Huisgen cycloaddition) protocol was performed onto *N*-(2-iodophenyl)-2-azidoacetamide as the acyclic precursor giving tricyclic 1,2,3-triazolo[5,1-*d*][1,4]benzodiazepin-2-ones. These target products were thus obtained through a three-step synthesis in variable yields depending upon the substituent placed onto the acetylenic counterpart. The influence of catalyst concentration, reaction temperature and reaction medium upon cycloadduct yields were also studied.

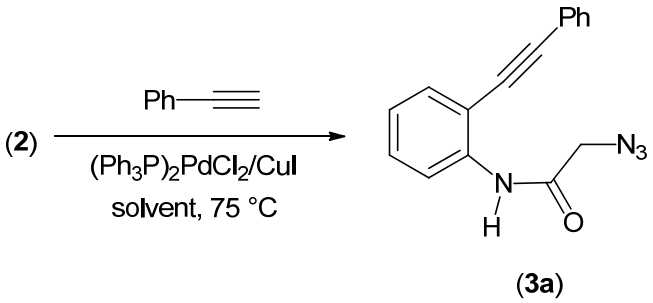
Due to their known anxiolytic,[1] anticonvulsant[2] and antidepressant[3] properties, triazolobenzodiazepines represent a valuable tool in organic synthesis[4] as well as in the field of drug discovery.[5] Intramolecular azide cycloadditions onto the triple carbon-carbon bond constitute the key step to annulated 1,2,3-triazoles.[6] Such chemistry allows the synthesis of relatively complex structures but does require the design and preparation of elaborate reactants containing both the azide moiety and the dipolarophilic counterpart. An easier and more useful access to this chemistry may be achieved by joining the effectiveness of palladium-catalysed coupling to the flexibility of intramolecular azide cycloaddition. The present paper is devoted to the latter combined strategy which is exploited in the three-step synthesis of 1,2,3-triazolo[5,1-*d*][1,4]benzodiazepine-2-ones[7] through the sequential Sonogashira/Huisgen protocol.

As the first step, acylation of 2-iodoaniline with bromoacetyl bromide gave *N*-(2-iodophenyl)-2-bromoacetamide (**1**) (Scheme 1). Subsequent treatment with sodium azide in aqueous acetone afforded *N*-(2-iodophenyl)-2-azidoacetamide (**2**) in 86% overall yield.



Scheme 1

Then, the Sonogashira coupling between (**2**) and phenylacetylene (Scheme 2) was optimised by varying reaction time and catalyst according to Table 1.



Scheme 2

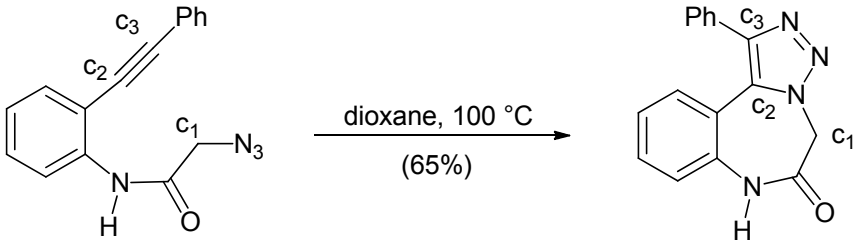
Table 1. Sonogashira coupling between (**2**) and phenylacetylene at 75 °C.

Entry	Solvent[a]	Time (h)	Catalyst[b] (mol. equiv.)	(**3a**) Yield (%)
1	dioxane	4	0.10	56
2	toluene	7	0.10	33
3	xylene	6	0.10	35
4	dimethylformamide	2	0.10	28
5	dioxane	3	0.05	67
6	toluene	4	0.05	35
7	xylene	4	0.05	38
8	dimethylformamide	1	0.05	33
9	dioxane	6	0.025	40
10	toluene	8	0.025	31
11	xylene	8	0.025	28
12	dimethylformamide	2	0.025	16

[a]0.05 M solution of (**2**). [b]$(Ph_3P)_2PdCl_2$/CuI 1:1.

Best results were obtained by using dry dioxane as the solvent and 1/20 mol equiv. of the catalyst as shown in Table 1, entry 5. Alkynylazide (**3a**) was thus obtained in the pure state in 67% yield; the absence of the cycloaddition product (**4a**) in the reaction mixture is reasonable since intramolecular azide cycloadditions to disubstituted alkynes are known to be relatively slow.[8]

Thermal cycloaddition (Huisgen reaction) was then performed by refluxing pure (**3a**) in dry dioxane (Scheme 3). After 7 h the desired cycloadduct (**4a**) was obtained in 65% yield (38% overall yield from 2-iodoaniline).



(**3a**) (**4a**)

Scheme 3

The main spectroscopic differences between (**3a**) and (**4a**) are given in Table 2. In particular, IR spectra showed the disappearance of the typical azide stretching band at 2120 cm^{-1},[9] while in the ^{13}C-NMR spectrum the couple of signals due to the two *sp* quaternary carbons C_2, C_3 of (**3a**) were replaced by the couple of singlets at lower fields due to the corresponding sp^2 carbons of the triazole nucleus.[10]

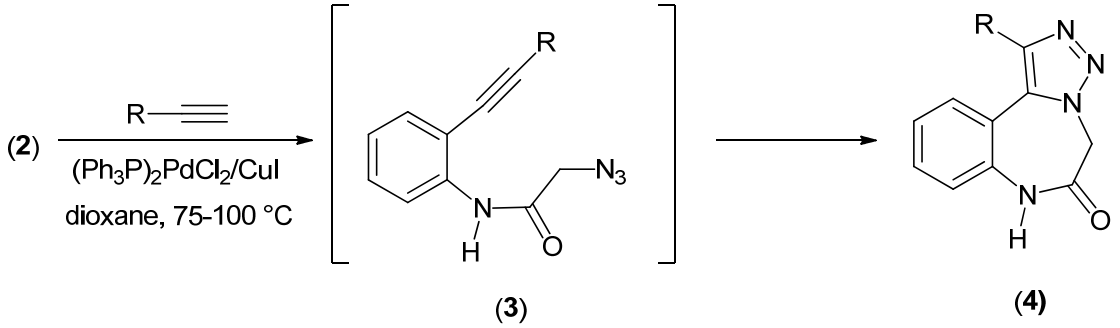
Table 2. Main spectroscopic features of compunds (**3a**) and (**4a**).

Spectroscopy	Product	
	(**3a**)[a]	(**4a**)[b]
IR (cm^{-1})	3335, 2120, 1680	3350, 1670
^{13}C NMR (δ, $CDCl_3$)	53.4 (t, C_1), 83.9 (s, C_2), 97.1 (s, C_3)	58.9 (t, C_1), 132.3 (s, C_2), 138.0 (s, C_3)

[a]Undistillable oil. [b]See Experimental section.

Having obtained product (**4a**), the subsequent step was the realisation of the sequential Sonogashira/ Huisgen transformation (**2** → **4**), thus making a real three-step synthesis of 1,2,3-triazolo[5,1-*d*][1,4]benzo-diazepin-2-ones (**4**) from 2-iodoaniline (Scheme 4). Reaction times and product yields are outlined in Table 3. To achieve this target, a solution of (**2**) in dry dioxane was heated to 75 °C in the presence of the catalyst and then refluxed. In the case of R = Ph, the intermediacy of (**3a**) was proven by simple TLC analysis of the

reaction mixture, while cycloadduct (**4a**) was obtained in the pure state after silica gel column chromatography and subsequent crystallisation with diisopropyl ether (see Experimental Section). Sequential Sonogashira/Huisgen reaction gave (**4a**) in 60% yield from (**2**), in other words the three-step synthesis of (**4a**) was fully satisfactory affording a 52% yield from 2-iodoaniline (Table 3, entry 1).



a: R = Ph, **b:** R = COOMe, **c:** R = CH_2OH, **d:** R = $(CH_2)_3OH$, **e:** R = CH(OH)Ph

Scheme 4

Table 3. Reaction times and product yields for the sequential reaction (**2**) → (**4**).[a,b]

Entry	R	Time[c] (h)	(**4**) Yield (%)[d]	2-Iodoaniline → (**4**) Yield (%)[e]
1	Ph	3 + 6	60	52
2	CO_2Me	4 + 6	35	30
3	CH_2OH	3 + 6	37	32
4	$(CH_2)_3OH$	5 + 6	79	68
5	CH(OH)Ph	5 + 6	7	6

[a]0.05 M solution of (**2**). [b]$(Ph_3P)_2PdCl_2$/CuI 1:1. [c]Time at 75 °C + time at 100 °C. [d]Isolation yields after silica gel column chromatography and crystallisation from diisopropyl ether. [e]Overall yield without isolation of the azide intermediate (**3**).

As far as the methyl propiolate is concerned (Table 3, entry 2) the sequential reaction had a disappointing outcome since the isolation yield of (**4b**) was 35%. Large amounts of unreacted (**2**) were recovered irrespective from the reaction time. Hence, it was decided to perform the Sonogashira coupling by heating at 75 °C a mixture of (**2**) and methyl propiolate. Alkynylazide (**3b**) was isolated in the pure state in 37% yield. Thermal cycloaddition (**3b**) → (**4b**) was exploited in refluxing dioxane and occurred in 94% yield. It is apparent that the extent of the Sonogashira/Huisgen protocol is limited by the coupling reaction. This result is not surprising by considering the electronic features of the methyl propiolate in comparison to the phenylacetylene and the mechanistic features of the Sonogashira coupling.[11] It is likely that an electron withdrawing group placed onto the acetylenic reactant may slow down the formation of the π-complex with

copper (I) which is involved as the initial step of the Sonogashira catalytic cycle. Similar considerations might be applied to the propargyl alcohol, see Table 3, entry **c**. In agreement to this picture, better results were obtained by interjecting sp^3 hybridised carbons between the triple bond and the hydroxyl group as in the case of pent-4-yn-1-ol (Table 3, entry **d**). The behaviour of 1-phenyl-2-propyn-1-ol, Table 3, entry **e**, could be dictated by adverse electronic and steric effects.

As a conclusion, it can be stated that the sequential Sonogashira/Huisgen protocol developed here constitutes a valuable shortcut to the synthesis of 1,2,3-triazolo[5,1-*d*][1,4]benzodiazepin-2-ones, limitations to this approach rely strongly upon the electronic features and the steric requirements of the acetylenic counterpart.

EXPERIMENTAL

General. Melting points were determined on a Büchi apparatus in open tubes and are uncorrected. IR spectra were recorded on a PerkineElmer 1725 X spectrophotometer. Mass spectra were determined on a VG-70EQ apparatus. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were taken with a Bruker AMX 300 instrument (in $CDCl_3$ solutions at room temperature). Chemical shifts are given as parts per million from tetramethylsilane. Coupling constants (*J*) values are given in hertz and are quoted to ±0.1 Hz consistently with NMR machine accuracy. All solvents and reagents were purified by standard technique or used as supplied from chemical sources as appropriate. Reagent chemicals were purchased from Aldrich Chemical Company Ltd. Solvents were dried and stored over 4Å molecular sieves prior to use.

Synthesis of *N*-(2-iodophenyl)-2-bromoacetamide (1). In a solution of bromoacetyl bromide (0.98 g, 4.8 mmol) in dry toluene (13.0 mL) was added triethylamine (0.49 g, 4.8 mmol) under stirring at room temperature. 2-Iodoaniline (1.00 g, 4.6 mmol) in dry toluene (5.0 mL) was added dropwise and the mixture was stirred at room temperature for 2 h. Water (15.0 mL) was added, the organic layer was separated and washed with aqueous 5% aqueous sodium hydrogen carbonate (5.0 mL), then with water (10.0 mL) and dried over sodium sulfate. Evaporation of the solvent at reduced pressure gave a residue which was crystallised with *i*Pr$_2$O affording pure *N*-(2-iodophenyl)-2-bromoacetamide (**1**) (1.43 g, 92%) as a white powder having mp 99 °C; IR (*Nujol*): 3250 (N-H), 1660 (>C=O) (cm^{-1}); ^{1}H-NMR: 3.79 (2H, s, -C<u>H</u>$_2$-), 6.62 (1H, dt, *J* = 7.8, 1.7, aromatic), 7.08 (1H, dt, *J* = 7.8, 1.8, aromatic), 7.53 (1H, dd, *J* = 7.8, 1.8, aromatic), 7.59 (1H, dd, *J* = 7.8, 1.6, aromatic), 8.75 (1H, br s, N-<u>H</u>); ^{13}C-NMR: 29.6 (t, -<u>C</u>H$_2$-), 90.1 (s, aromatic), 121.8 (d, aromatic), 126.7 (d, aromatic), 129.1 (d, aromatic), 137.4 (s, aromatic), 139.0 (d, aromatic), 163.7 (s, >C=O); MS: 340 *m/z* (M$^+$). *Anal*. Calcd for C_8H_7NOBrI: C, 28.26; H, 2.08; N, 4.12. Found: C, 28.30; H, 2.11; N, 4.06.

Synthesis of *N*-(2-iodophenyl)-2-azidoacetamide (2). A solution of sodium azide (1.04 g, 8.0 mmol) in water (4.0 mL) was added dropwise to a solution of *N*-(2-iodophenyl)-2-bromoacetamide **(1)** (1.08 g, 3.2 mmol) in dry acetone (16.0 mL) under stirring at room temperature. After 40 min the mixture was partially evaporated under reduced pressure and water (15.0 mL) was added. The aqueous residue was extracted with EtOAc (3 x 20 mL) and the organic layer was dried over sodium sulfate. Evaporation of the solvent at reduced pressure gave a residue which was crystallised with iPr$_2$O affording pure *N*-(2-iodophenyl)-2-azidoacetamide (**2**) (0.89 g, 93%) as a yellow powder having mp 83-84 °C (decomposes); IR (*Nujol*): 3250 (N-H), 2120 (-N_3), 1660 (>C=O) (cm^{-1}); ^{1}H-NMR: 4.18 (2H, s, -C$\underline{H}_2$-), 6.79 (1H, dt, J = 7.7, 1.8, aromatic), 7.33 (1H, dt, J = 7.7, 1.5, aromatic), 7.78 (1H, dd, J = 7.7, 1.8, aromatic), 8.23 (1H, dd, J = 7.7, 1.8, aromatic), 8.45 (1H, br s, N-$\underline{H}$); ^{13}C-NMR: 53.1 (t, -$\underline{C}H_2$-), 90.0 (s, aromatic), 121.8 (d, aromatic), 126.5 (d, aromatic), 129.2 (d, aromatic), 137.2 (s, aromatic), 138.9 (d, aromatic), 164.7 (s, >$\underline{C}$=O); MS: 302 *m/z* (M$^+$). *Anal*. Calcd for $C_8H_7N_4OI$: C, 31.81; H, 2.34; N, 18.55. Found: C, 31.78; H, 2.36; N, 18.59.

General procedure for the Sonogashira coupling between (2) and phenylacetylene. In a solution of *N*-(2-iodophenyl)-2-azidoacetamide (**2**) (0.50 g, 1.7 mmol) in dry solvent (34.0 mL) were added phenylacetylene (0.17 g, 1.7 mmol), triethylamine (0.21 g, 2.0 mmol), copper iodide and *bis*(triphenyl-phosphine)palladium (II) dichloride (see Table 1) under nitrogen at room temperature. The mixture was warmed to 75 °C for the time indicated in Table 1, then filtered over a celite pad. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column with hexane/EtOAc 3:1. Unreacted (**2**) was eluted first, followed by *N*-(2-phenylethynyl)phenyl-2-azidoacetamide (**3a**) as an undistillable oil in the yields reported in the Table 1. IR (*Nujol*): 3335 (N-H), 2120 (-N_3), 1680 (>C=O) (cm^{-1}); ^{1}H-NMR: 4.21 (2H, s, -C$\underline{H}_2$-), 7.15 (1H, dt, J = 7.8, 1.7, aromatic), 7.3-7.6 (8H, aromatics), 8.43 (1H, dd, J = 7.8, 1.8, aromatic), 9.15 (1H, br s, N-$\underline{H}$); ^{13}C-NMR: 53.4 (t, -$\underline{C}H_2$-), 83.9 (s, Ar-$\underline{C}$≡), 97.1 (s, ≡$\underline{C}$-Ph), 120.0-139.0 (aromatics), 163.8 (s, >$\underline{C}$=O); MS: 276 *m/z* (M$^+$). *Anal*. Calcd (%) for $C_{16}H_{12}N_4O$: C, 69.55; H, 4.38; N, 20.28. Found: C, 69.59; H, 4.41; N, 20.33.

Synthesis of *N*-(2-methoxycarbonylethynyl)phenyl-2-azidoacetamide (3b). In a solution of *N*-(2-iodophenyl)-2-azidoacetamide (**2**) (0.50 g, 1.70 mmol) and methyl propiolate (0.14 g, 1.70 mmol) in dry dioxane (26.0 mL) were added 0.20 g (274 μL, 2.00 mmol) of triethylamine, 31.0 mg (85.0 μmol) of copper (I) iodide and 62 mg (85.0 μmol) of *bis*(triphenylphosphine)palladium (II) dichloride under nitrogen at room temperature. The mixture was warmed at 75 °C for 5 h. The crude was filtered over a celite pad and the solvent was evaporated under reduced pressure. The residue was chromatographed on a silica gel column with hexane/EtOAc 3:1. Unreacted (**2**) was eluted first, followed by *N*-(2-methoxycarbonyl-

ethynyl)phenyl-2-azidoacetamide (**3b**) (0.16 g, 37%) as an undistillable oil; IR (*Nujol*): 3330 (N-H), 2120 (-N_3), 1730, (ester >C=O), 1680 (amide >C=O) (cm^{-1});. ^{1}H-NMR: 3.93 (3H, s, -C<u>H</u>$_3$), 4.16 (2H, s, -C<u>H</u>$_2$-), 7.14 (1H, dt, *J* = 7.8, 1.2, aromatic), 7.35 (1H, dt, *J* = 8.2, 1.1, aromatic), 7.83 (1H, dd, *J* = 8.2, 1.1, aromatic), 8.18 (1H, dd, *J* = 7.8, 1.2, aromatic), 8.30 (1H, br s, N-<u>H</u>); ^{13}C-NMR: 49.8 (q, -<u>C</u>H$_3$), 55.8 (t, -<u>C</u>H$_2$-), 83.5 (s, Ar-<u>C</u>≡), 97.8 (s, ≡<u>C</u>-COOMe), 118.1 (d, aromatic), 122.6 (d, aromatic), 128.0-132.0 (aromatics), 138.0 (s, aromatic), 165.2 (s, amide ><u>C</u>=O), 165.2 (s, ester ><u>C</u>=O); MS: 258 *m/z* (M^+). *Anal.* Calcd for $C_{12}H_{10}N_4O_3$: C, 55.81; H, 3.90; N, 31.70. Found: C, 55.85; H, 3.88; N, 31.74.

Intramolecular cycloaddition of *N*-(2-phenylethynyl)phenyl-2-azidoacetamide (3a). A solution of *N*-(2-phenylethynyl)phenyl-2-azidoacetamide (**3a**) (130 mg, 0.47 mmol) in dry dioxane (9.5 mL) was refluxed under nitrogen for 7 h. The solvent was evaporated under reduced pressure and the residue was crystallised from *i*Pr_2O ether giving 2-phenyl-1,2,3-triazolo[5,1-*d*][1,4]benzodiazepin-2-one (**4a**) (85 mg, 65%) as a white powder having mp 218 °C; IR (*Nujol*): 3350 (N-H), 1670 (>C=O) (cm^{-1}); ^{1}H-NMR: 5.63 (2H, s, -C<u>H</u>$_2$-), 7.33 (1H, dt, *J* = 8.0, 1.1, aromatic), 7.40-7.78 (7H, m, aromatics), 8.14 (1H, dd, *J* = 8.3, 1.0, aromatic), 9.20 (1H, br s, N-<u>H</u>); ^{13}C-NMR: 58.9 (t, -<u>C</u>H$_2$-), 118.4 (d, aromatic), 123.7 (d, aromatic), 127.1-130.8 (aromatics), 132.3 (s, =<u>C</u>-N<), 138.0 (s, =<u>C</u>-N=), 168.9 (s, ><u>C</u>=O); MS: 276 *m/z* (M^+). *Anal*. Calcd for $C_{16}H_{12}N_4O$: C, 69.55; H, 4.38; N, 20.28. Found: C, 69.53; H, 4.43; N, 20.36.

Intramolecular cycloaddition of *N*-(2-methoxycarbonylethynyl)phenyl-2-azidoacetamide (3b). A solution of *N*-(2-methoxycarbonylethynyl)phenyl-2-azidoacetamide (**3b**) (120 mg, 0.46 mmol) in dry dioxane (9.4 mL) was refluxed under nitrogen for 6 h. The solvent was evaporated under reduced pressure and the residue was crystallised from *i*Pr_2O ether giving 2-methoxycarbonyl-1,2,3-triazolo[5,1-*d*][1,4]benzodiazepin-2-one (**4b**) (113 mg, 94%) as a pale yellow powder having mp 164-166 °C; IR (*Nujol*): 3345 (N-H), 1735 (ester >C=O), 1670 (lactam >C=O); ^{1}H-NMR: 3.91 (3H, s, -C<u>H</u>$_3$), 5.68 (2H, s, -C<u>H</u>$_2$-), 7.18 (1H, dt, *J* = 7.8, 1.2, aromatic), 7.36 (1H, dt, *J* = 8.2, 1.1, aromatic), 7.56 (1H, dd, *J* = 8.2, 1.1, aromatic), 8.15 (1H, dd, *J* = 7.8, 1.2, aromatic), 9.30 (1H, br s, N-<u>H</u>); ^{13}C-NMR: 49.6 (q, -<u>C</u>H$_3$), 59.3 (t, -<u>C</u>H$_2$-), 118.0 (d, aromatic), 124.2 (d, aromatic), 128.0-131.0 (aromatics), 132.5 (s, =<u>C</u>-N<), 138.8 (s, =<u>C</u>-N=), 166.7 (s, lactam >C=O); 168.9 (s, ester ><u>C</u>=O); MS: 258 *m/z* (M^+). *Anal*. Calcd for $C_{12}H_{10}N_4O_3$: C, 55.81; H, 3.90; N, 31.70. Found: C, 55.87; H, 3.93; N, 31.78.

Sequential synthesis of 2-substituted-1,2,3-triazolo[5,1-*d*][1,4]benzodiazepin-2-ones (4). General procedure. In a solution of *N*-(2-iodophenyl)-2-azidoacetamide (**2**) (0.40 g, 1.32 mmol) and 1.32 mmol of the appropriate alkyne in dry dioxane (26.0 mL) was added 0.16 g (216 μL, 1.60 mmol) of triethylamine, 24.0 mg (66.0 μmol) of copper (I) iodide and 48 mg (66.0 μmol) of *bis*(triphenylphosphine)palladium (II)

dichloride under nitrogen at room temperature. The mixture was warmed at 75 °C and then refluxed for the time indicated in Table 3. The crude was filtered over a celite pad and the solvent was evaporated under reduced pressure. The residue was chromatographed on a silica gel column with hexane/EtOAc 3:1. Unreacted (**2**) was eluted first, followed by 2-substituted-1,2,3-triazolo[5,1-*d*][1,4]benzodiazepin-2-one (**4**) as a solid after crystallisation with *i*Pr_2O.

2-Phenyl-1,2,3-triazolo[5,1-*d*][1,4]benzodiazepin-2-one (**4a**) (0.22 g, 60%).

2-Methoxycarbonyl-1,2,3-triazolo[5,1-*d*][1,4]benzodiazepin-2-one (**4b**) (0.12 g, 35%).

2-Hydroxymethyl-1,2,3-triazolo[5,1-*d*][1,4]benzodiazepin-2-one (**4c**) (0.11 g, 37%). White powder, mp 151-154 °C; IR (*Nujol*): 3450 (O-H), 3340 (N-H), 1670 (>C=O) (cm^{-1}); ^{1}H-NMR: 2.15 (1H, br s, -OH), 3.90 (2H, s, -CH_2OH), 5.62 (2H, s, -CH_2-), 7.09 (1H, dt, *J* = 7.9, 1.1, aromatic), 7.33 (1H, dt, *J* = 8.2, 1.4, aromatic), 7.42 (1H, dd, *J* = 7.9, 1.1, aromatic), 8.36 (1H, dd, *J* = 8.2, 1.4, aromatic), 8.90 (1H, br s, N-H); ^{13}C-NMR: 51.5 (t, -CH_2OH), 53.4 (t, -CH_2-), 119.3 (d, aromatic), 124.1 (d, aromatic), 129.9 (d, aromatic), 135.1 (d, aromatic), 132.1 (s, =C-N<), 138.1 (s, =C-N=), 164.5 (s, >C=O); MS: 230 *m/z* (M^+). *Anal*. Calcd for $C_{11}H_{10}N_4O_2$: C, 57.39; H, 4.38; N, 24.34. Found: C, 57.43; H, 4.41; N, 24.38.

2-(3-Hydroxy)propyl-1,2,3-triazolo[5,1-*d*][1,4]benzodiazepin-2-one (**4d**) (0.27 g, 79%). White powder, mp 143-147 °C; IR (*Nujol*): 3480 (O-H), 3310 (N-H), 1680 (>C=O) (cm^{-1}); ^{1}H-NMR: 1.80 (1H, br s, -OH), 1.89-1.98 (2H, m, -CH_2-), 2.67 (2H, t, *J* = 7.0, -CH_2-), 3.86 (2H, t, *J* = 7.0, -CH_2OH), 5.60 (2H, s, -CH_2CO-), 7.07 (1H, dt, *J* = 7.9, 1.1, aromatic), 7.29 (1H, dt, *J* = 8.2, 1.3, aromatic), 7.41 (1H, dd, *J* = 7.9, 1.1, aromatic), 8.36 (1H, dd, *J* = 8.2, 1.3, aromatic), 9.0 (1H, br s, N-H); ^{13}C-NMR: 16.1 (t, -CH_2-), 31.3 (t, -CH_2-), 49.2 (t, -CH_2OH), 54.3 (t, -CH_2CO-), 119.1 (d, aromatic), 124.0 (d, aromatic), 128.8 (s, aromatic), 129.0 (d, aromatic), 131.5 (d, aromatic), 132.1 (s, =C-N<), 137.9 (s, =C-N=), 164.5 (s, >C=O); MS: 258 *m/z* (M^+). *Anal*. Calcd for $C_{13}H_{14}N_4O_2$: C, 60.46; H, 5.64; N, 21.69. Found: C, 60.50; H, 5.61; N, 21.74.

2-(Phenyl)hydroxymethyl-1,2,3-triazolo[5,1-*d*][1,4]benzodiazepin-2-one (**4e**) (27 mg, 7%). White powder, mp 178-181 °C; IR (*Nujol*): 3460 (O-H), 3330 (N-H), 1680 (>C=O) (cm^{-1}); ^{1}H-NMR: 2.06 (1H, br s, -OH), 4.37 (1H, s, -CH(OH)-), 5.68 (2H, s, -CH_2CO-), 7.07 (1H, dt, *J* = 7.9, 1.1, aromatic), 7.12-7-40 (6H, m, aromatics), 7.48 (1H, dd, *J* = 7.9, 1.1, aromatic), 8.36 (1H, dd, *J* = 8.2, 1.3, aromatic), 8.85 (1H, br s, N-H); ^{13}C-NMR: 52.7 (d, -CH-OH), 56.2 (t, -CH_2-), 116.4 (d, aromatic), 123.0 (d, aromatic), 126.8-132.0 (aromatics), 133.1 (s, =C-N<), 138.4 (s, =C-N=), 166.7 (s, >C=O); MS: 306 *m/z* (M^+). *Anal*. Calcd for $C_{17}H_{14}N_4O_2$: C, 66.66; H, 4.61; N, 18.29. Found: C, 66.70; H, 4.59; N, 18.33.

ACKNOWLEDGEMENTS

Thanks are due to the student Laura Marino for her ability in carrying out some experiments and to Dr. Lara de Benassuti, University of Milan, who accomplished NMR spectra.

REFERENCES

1. P. J. Snyder, J. Werth, B. Giordani, A. F. Caveney, D. Feltner, and P. Maruff, *Hum. Psychopharmacol. Clin. Exp.*, 2005, **20**, 263.
2. (a) J. Levine, D. P. Cole, K. N. Roy Chengappa, and S. Gerson, *Depress. Anxiety*, 2001, **14**, 94; (b) G. L. Post, R. O. Patrick, J. E. Crowder, J. Houston, J. M. Ferguson, R. J. Bielski, L. Bailey, H. G. Pearlman, V. S. Shu, and M. W. Pierce, *J. Clin. Psychopharmacol.*, 1991, **11**, 249.
3. D. J. Greenblatt, J. S. Harmatz, L. Shapiro, N. Engelhardt, T. A. Gouthro, and T. A. Shader, *New. Engl. J. Med.*, 1991, **324**, 1691.
4. For Books chapters: (a) P. A. Wade, 'Comprehensive Organic Synthesis'; ed. by B. M. Trost, Pergamon Press, New York, 1992; Vol. 4, Ch. 4/10, p. 1111; (b) A. Padwa, '1,3-Dipolar Cycloaddition Chemistry'; ed. by A. Padwa, Wiley-Interscience, New York, 1984; Vol. 2, p. 277; For general reviews: (c) K. V. Gothelf and K. A. Jørgensen, *Chem. Rev*., 1998, **98**, 863; (d) S. Karlsson and E.-H. Högberg, *Org. Prep. Proced. Int*., 2001, **33**, 1032; (e) H. Pellissier, *Tetrahedron*, 2007, **63**, 3235.
5. (a) L. Prut and C. Belzung, *Eur. J. Pharmacol*., 2003, **463**, 3; (b) P. D. Garzone and P. D. Kroboth, *Clin. Pharmacokin*., 1989, **16**, 337; (c) A. D. Rudzik, J. B. Hester, A. H. Tang, R. N. Straw, and W. Friis, *Benzodiazepines*, 1973, 285.
6. (a) K. Majumdar and K. Ray, *Synthesis*, 2011, 3767; (b) A. J. M. Burrell and I. Coldham, *Curr. Org. Synth*., 2010, **7**, 312; (c) V. Nair and T. D. Suja, *Tetrahedron*, 2007, **63**, 12247; (d) S. Braese, C. Gil, K. Knepper, and V. Zimmermann, *Angew. Chem. Int. Ed*., 2005, **44**, 5188.
7. K. Majumdar, K. Ray, S. Ganai, and T. Ghosh, *Synthesis*, 2010, 858.
8. (a) R. Huisgen, '1,3-Dipolar Cycloaddition Chemistry'; ed. by A. Padwa; John Wiley & Sons, New York, 1984; Vol. 1, Ch. 1, p. 1; (b) R. Huisgen, G. Szeimnies, and L. Moebius, *Chem. Ber*., 1967, **100**, 2494; (c) R. Huisgen, *Pure Appl. Chem*., 1989, **61**, 613; (d) L. Garanti, G. Molteni, and G. Broggini, *J. Chem. Soc., Perkin Trans. 1*, 2001, 1816; (e) G. Broggini, G. Molteni, and G. Zecchi, *Synthesis*, 1995, 647.
9. L. J. Bellamy, 'The Infra-Red Spectra of Complex Molecules'; Methuen & CO, Ltd., London, 1958; Ch. 16, p. 263.
10. (a) T. J. Batterham, 'NMR Spectra of Simple Heterocycles'; Krieger Publishing Company, Malabar, Florida, 1980; p. 355; (b) ^{1}H-NMR spectra of 2,5-benzodiazepin-4-ones: A. Stempel, I. Douvan, and L. H. Sternbach, *J. Org. Chem*., 1968, **33**, 2963.
11. (a) T. J. J. Müller, *Synthesis*, 2012, 159; (b) R. Chinchilla and C. Nájera, *Chem. Soc. Rev*., 2011, **40**, 5084; (c) M. Beaupèrin, E. Fayad, R. Amardeil, H. Cattey, P. Richard, S. Brandés, P. Meunier, and J.-C. Hierso, *Organometallics*, 2008, **27**, 2506; (d) M. Beaupèrin, A. Job, H. Cattey, S. Royer, P. Meunier, and J.-C. Hierso, *Organometallics*, 2010, **29**, 2815.