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THIENO[2,3-*f*]TRIAZOLO[1,5-*a*][1,4]DIAZEPINES AND THIENO[2,3-*f*]-TRIAZOLO[1,5-*a*][1,4]OXAZEPINES FROM AZIDE CYCLOADDITION

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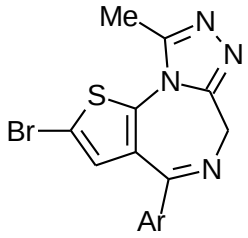
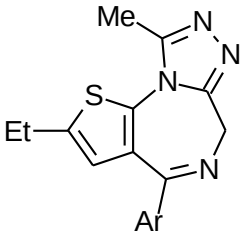
Abstract – Intermolecular dipolar cycloadditions between 2-methoxycarbonyl-3-thenylazide (**3**) and monosubstituted dipolarophiles bearing a triple carbon-carbon bond were exploited in a three step synthesis of the title compounds. The intramolecular cycloaddition of substituted thenylazide (**11**) was also carried out in the two-step synthesis of the thieno[2,3-*f*][1,2,3]triazolo[1,5-*a*]-[1,4]diazepine derivative (**8**).

It is fair to say that azide cycloadditions have experienced a rebirth since 2001, after the "click" chemistry approach was disclosed.[1] In the "click" conditions, azide-alkyne cycloadditions are carried out in aqueous media in the presence of Cu (I) catalyst giving only the 4-substituted regioisomer.[2] This regioselectivity is surely an interesting feature of this novel azide-alkyne cycloaddition but can constitute a severe limitation when the 5-substituted 1,2,3-triazole represent the desired target.[3] In this latter case the classic Huisgen cycloaddition still seems to be the choice route notwithstanding a mixture of regioisomers are often obtained.[4]

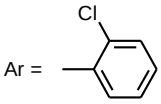
Some years ago, we carried out the synthesis of the thieno[2,3-*f*][1,2,3]triazolo[5,1-*c*][1,4]diazepine skeleton by intramolecular cycloaddition of substituted acylazides.[5] Unfortunately, we were able to isolate the above heterocyclic system only in one case and with moderate yield due to the ease of the acylazide moiety to undergo the Curtius rearrangement.[6] In the present paper we undertook the investigation of intermolecular cycloadditions between 2-methoxycarbonyl-3-thenylazide (**3**) and monosubstituted dipolarophiles bearing a triple carbon-carbon bond with the aim to synthesize the unreported thieno[2,3-*f*][1,2,3]triazolo[1,5-*a*][1,4]diazepine skeleton. For instance, some thienotriazolo diazepines[7] like Brotizolam and Etizolam belongs to a new class of diazepines which possesses amnesic, anxiolytic, anticonvulsant, hypnotic, sedative and skeletal muscle relaxant properties.[8,9]



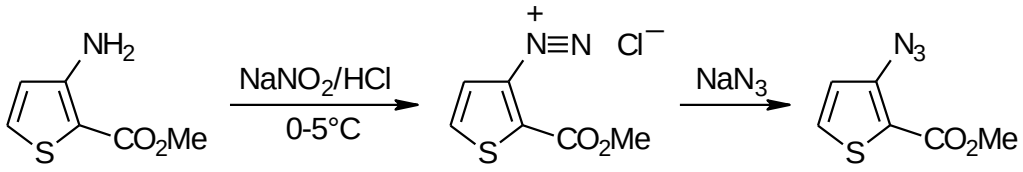
BROTIZOLAM



ETIZOLAM



2-Methoxycarbonyl-3-thenylazide (**3**)[10] was readily prepared from the commercially available aminoester (**1**) by diazotisation followed by treatment with sodium azide (see Scheme 1).



1 **2** **3** (87%)

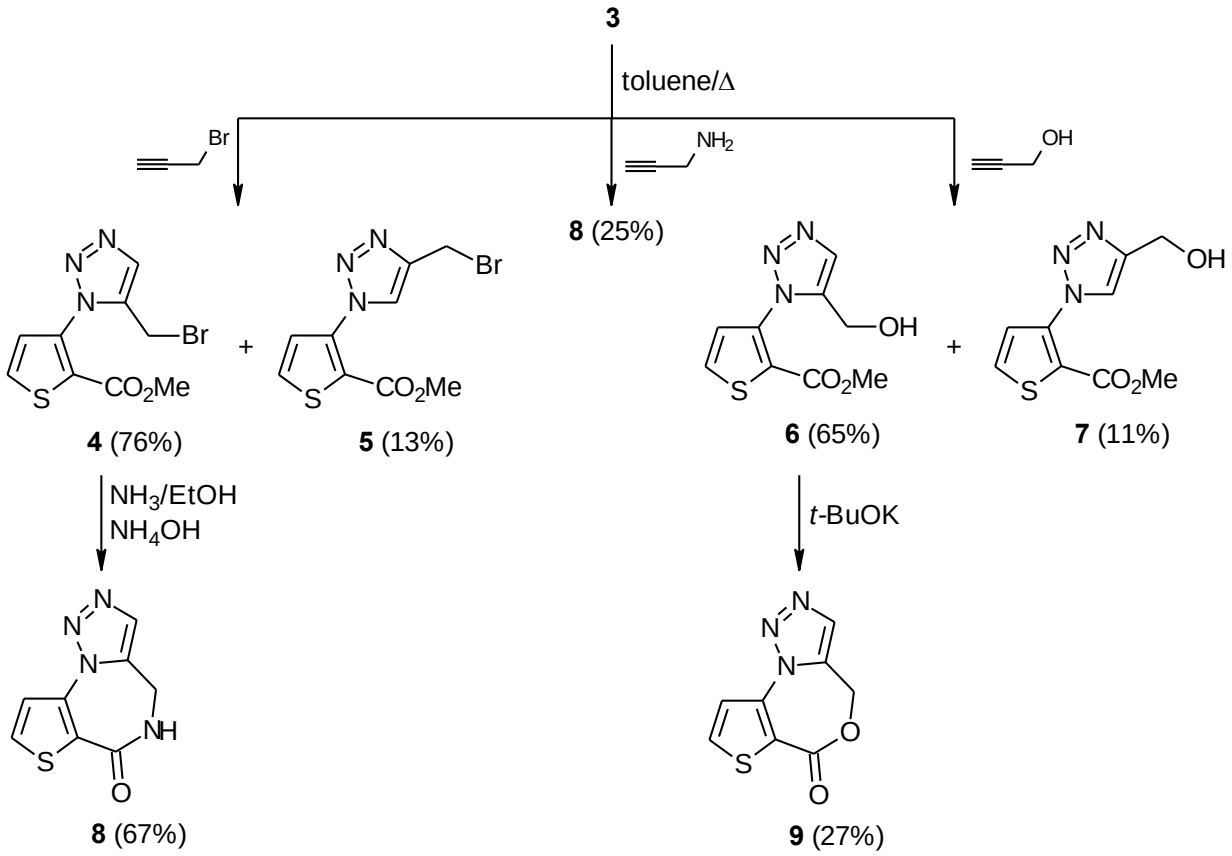
Scheme 1

Azide (**3**) was submitted to cycloaddition with propargyl bromide, propargyl alcohol and propargylamine in hot toluene as depicted in the Scheme 2 giving respectively the corresponding 1,2,3-triazole derivatives (**4**)-(**7**) and the tricyclic target compound (**8**). The structure of all new compounds were firmly established by elemental analyses and spectral data, including ^{1}H and ^{13}C NMR, IR, and MS spectrometry (see EXPERIMENTAL).

The extent of the cycloaddition was strongly dependent on the electronic features of dipolarophilic acetylenes. While propargyl bromide and propargyl alcohol gave rise to a clean reaction, large amounts of tarry material and poor cycloadduct yield was observed in the reaction with propargylamine. With the exception of the latter dipolarophile, in the remaining cases a mixture of regioisomeric 1,2,3-triazole derivatives was obtained. The predominance of 5-substituted 1,2,3-triazoles (**4**) and (**6**) reflects the usual HOMO-LUMO dipole control of the azide;[11] furthermore, it can be noted that the regioisomeric ratio 85:15 was operating in both cases.

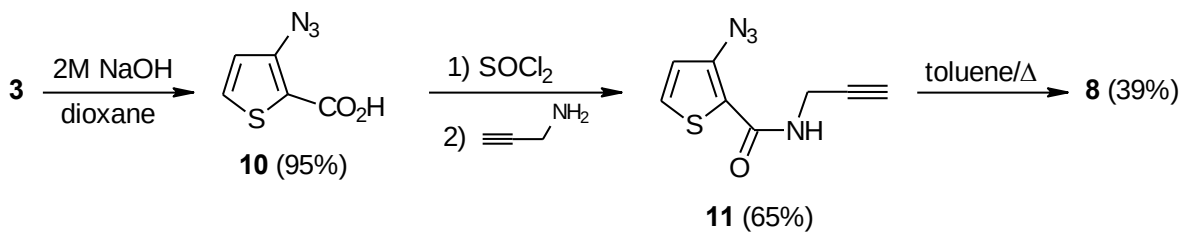
As the final step of our synthesis, the 1,4-diazepine ring closure of major cycloadducts (**4**) and (**6**) was carried out by internal nucleophilic attack. The required nucleophilic species were generated by treating (**4**) with ammonia and (**6**) with potassium *ter*-butoxide. No intermediates were isolated since spontaneous ring closure to tricyclic products (**8**) and (**9**) just occurred. By contrast, the transformation (**6**) → (**9**) failed under acidic catalytic conditions (PTSA and PPA) since unreacted (**6**) was recovered.

The one-pot cycloaddition between (**3**) and propargylamine occurred with 25% overall yield. To this respect, better results were obtained from the two-step procedure involving the intermediacy of (**4**) since the overall yield of the transformation (**3**) → (**4**) → (**8**) was 51%.



Scheme 2

To this point, we perceived the opportunity to obtain the tricyclic product (**8**) *via* intramolecular cycloaddition of the substituted thenylazide (**11**) (Scheme 3). The latter compound was readily prepared from (**3**) through alkaline hydrolysis to 2-hydroxycarbonyl-3-thenylazide (**10**)[12] and subsequent treatment with thionyl chloride and propargylamine. By refluxing (**11**) in toluene, product (**8**) was recovered with 39% yield, i.e. with 24% overall yield from (**3**). This disappointing result confirms that the route (**3**) → (**4**) → (**8**) is the best way to access the desired tricycle (**8**).



Scheme 3

The synthesis of the novel thieno[2,3-*f*][1,2,3]triazolo[1,5-*a*][1,4]diazepine and thieno[2,3-*f*][1,2,3] triazolo[1,5-*a*][1,4]oxazepine skeletons of potential interest as pharmacophoric agent have been carried out in the multi-gram scale by the azide-alkyne cycloaddition as the key step. The one-pot route (**3**) → (**8**) and the intramolecular cycloaddition of thenylazide (**11**) gave poor results, while smooth and clean intermolecular cycloadditions were experienced with propargyl bromide and allyl alcohol.

EXPERIMENTAL

Melting points were determined with a Büchi apparatus in open tubes and are uncorrected. IR spectra were recorded with a Perkin-Elmer 1725 X spectrophotometer. MS spectra were determined with 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 ppm from tetramethylsilane and *J* values are given in Hz.

2-Methoxycarbonyl-3-aminothiophene (**1**) was used as purchased by Aldrich without any further purification.

2-Methoxycabonyl-3-thenylazide (3). Sodium nitrite (1.54 g, 22.3 mmol) was added portionwise to a solution of 2-methoxycarbonyl-3-aminothiophene (**1**) (2.50 g, 15.9 mmol) in 1N aqueous hydrochloric acid (90 mL) under stirring and cooling at 0 °C. After the addition of methyl *ter*-butyl ether (70 mL), sodium azide (1.24 g, 19.1 mmol) was added portionwise under vigorous stirring and ice-cooling. After 1 h the organic layer was separated, washed with 5% aqueous sodium hydrogencarbonate (2 x 30 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was crystallised from diisopropyl ether to give 2.53 g, 87% of pure 2-methoxycarbonyl-3-thenylazide (**3**) as yellow needles having mp 68-69 °C; IR (Nujol): 2130, 1700 (cm^{-1}); ^{1}H-NMR: 3.92 (3H, s), 6.95 (1H, d, *J*=5.4), 7.50 (1H, d, *J*=5.4); MS: 183 *m/z* (M^+). *Anal.* Calcd for $C_6H_5N_3O_2S$: C, 39.34; H, 2.75; N, 22.95. Found: C, 39.29; H, 2.77; N, 23.02.

Cycloaddition between 2-methoxycabonyl-3-thenylazide (3) and propargyl bromide. A solution of 2-methoxycabonyl-3-thenylazide (**3**) (1.24 g, 6.8 mmol) and propargyl bromide (4.05 g, 34.0 mmol) was heated at 85 °C in dry toluene (70 mL) under nitrogen atmosphere for 12 h. Evaporation of the solvent gave a residue that was chromatographed on a silica gel column with CH_2Cl_2-EtOAc 10 : 1. First fractions contained 1-[(2-metoxycarbonyl)-3-thenyl]-5-bromomethyl-1,2,3-triazole (**4**) (1.56 g, 76%) as pale yellow needles having mp 118 °C (from diisopropyl ether); IR (Nujol): 1740 (cm^{-1}); ^{1}H-NMR: 3.80 (3H, s), 4.43 (2H, s), 7.40 (1H, d, *J*=5.4), 7.75 (1H, d, *J*=5.4), 7.87 (1H, s); ^{13}C NMR: 21.3 (t), 52.5 (q), 125.6-131.1, 138.0 (s), 138.7 (s), 143.7 (s), 160.9 (s); MS: 302 *m/z* (M^+). *Anal.* Calcd for $C_9H_8BrN_3O_2S$:

C, 35.77; H, 2.67; N, 13.91. Found: C, 35.72; H, 2.70; N, 13.97.

Further elution gave 1-[(2-metoxycarbonyl)-3-thenyl]-4-bromomethyl-1,2,3-triazole (**5**) (0.27 g, 13%) as pale yellow needles having mp 88 °C (from diisopropyl ether); IR (Nujol): 1735 (cm^{-1}); ^{1}H-NMR: 3.85 (3H, s), 4.65 (2H, s), 7.52 (1H, d, *J*=5.4), 7.61 (1H, d, *J*=5.4), 8.45 (1H, s); ^{13}C NMR: 20.1 (t), 55.7 (q), 123.2-131.8, 135.4 (s), 137.7 (s), 140.3 (s), 158.0 (s); MS: 302 *m/z* (M^+). *Anal.* Calcd for $C_9H_8BrN_3O_2S$: C, 35.77; H, 2.67; N, 13.91. Found: C, 35.70; H, 2.63; N, 13.99.

Cycloaddition between 2-methoxycabonyl-3-thenylazide (3) and propargyl alcohol. A solution of 2-methoxycabonyl-3-thenylazide (**3**) (1.50 g, 8.2 mmol) and propargyl alcohol (2.30 g, 41.0 mmol) was refluxed in dry toluene (65 mL) under nitrogen atmosphere for 14 h. Evaporation of the solvent under reduced pressure gave a residue that was chromatographed on a silica gel column with CH_2Cl_2-EtOAc 10 : 1.

First fractions contained 1-[(2-metoxycarbonyl)-3-thenyl]-5-hydroxymethyl-1,2,3-triazole (**6**) (1.27 g, 65%) as white amorphous powder having mp 98 °C (from diisopropyl ether); IR (Nujol): 3250, 1735 (cm^{-1}); ^{1}H-NMR: 3.20 (1H, br s), 3.88 (3H, s), 5.32 (2H, s), 7.55 (1H, d, *J*=5.4), 7.65 (1H, d, *J*=5.4), 7.83 (1H, s); ^{13}C NMR: 20.6 (t), 62.1 (q), 128.8-132.3, 136.5 (s), 140.2 (s), 144.6 (s), 158.7 (s); MS: 239 *m/z* (M^+). *Anal.* Calcd for $C_9H_9N_3O_3S$: C, 45.18; H, 3.79; N, 17.57. Found: C, 45.23; H, 3.82; N, 17.64.

Further elution gave 1-[(2-metoxycarbonyl)-3-thenyl]-4-hydroxymethyl-1,2,3-triazole (**7**) (0.22 g, 11%) as white amorphous powder having mp 76 °C (from diisopropyl ether); IR (Nujol): 3180, 1720 (cm^{-1}); ^{1}H-NMR: 2.90 (1H, br s), 3.90 (3H, s), 4.93 (2H, s), 7.56 (1H, d, *J*=5.3), 7.66 (1H, d, *J*=5.3), 8.41 (1H, s); ^{13}C NMR: 23.5 (t), 57.9 (q), 126.6-130.3, 132.5 (s), 137.1 (s), 142.0 (s), 161.7 (s); MS: 239 *m/z* (M^+). *Anal.* Calcd for $C_9H_9N_3O_3S$: C, 45.18; H, 3.79; N, 17.57. Found: C, 45.21; H, 3.84; N, 17.66.

Cycloaddition between 2-methoxycabonyl-3-thenylazide (3) and propargylamine. A solution of 2-methoxycabonyl-3-thenylazide (**3**) (1.10 g, 6.0 mmol) and propargylamine (1.65 g, 30.0 mmol) was heated at 80 °C in dry toluene (60 mL) under nitrogen atmosphere for 13 h. Evaporation of the solvent under reduced pressure gave a residue that was chromatographed on a silica gel column with CH_2Cl_2-EtOAc 7 : 3. Subsequent crystallisation with hexane-toluene gave 0.31 g, 25% of pure 2-oxo-4*H*-thieno[2,3-*f*][1,2,3]triazolo[1,5-*a*][1,4]diazepine (**8**) as pale yellow amorphous powder having mp 77 °C. IR (Nujol): 3350, 1670 (cm^{-1}); ^{1}H-NMR: 4.08 (2H, s), 5.85 (1H, br s), 7.12 (1H, d, *J*=5.4), 7.58 (1H, d, *J*=5.4), 7.89 (1H, s); ^{13}C NMR: 37.5 (t), 125.4-129.7, 140.1 (s), 146.8 (s), 150.1 (s), 163.9 (s); MS: 206 *m/z* (M^+). *Anal.* Calcd for $C_8H_6N_4OS$: C, 46.60; H, 2.93; N, 27.19. Found: C, 46.65; H, 2.99; N, 27.26.

Cyclisation to thieno[2,3-*f*][1,2,3]triazolo[1,5-*a*][1,4]diazepine (8). A solution of (**4**) (1.12 g, 3.7 mmol) in 2M ethanolic ammonia (35 mL, 70.0 mmol) and 30% aqueous NH_4OH (10 mL, 85.7 mmol) was stirred at room temperature for 48h. Evaporation of the solvent gave a residue that was extracted with CH_2Cl_2 (70 mL). The organic layer was dried over sodium sulfate, the solvent was removed under reduced pressure and the residue was crystallised with diisopropyl ether giving 0.51 g, 67% of pure (**8**).

Cyclisation to thieno[2,3-*f*][1,2,3]triazolo[1,5-*a*][1,4]oxazepine (9). To a solution of (**6**) (1.05 g, 4.4 mmol) in anhydrous THF (30 mL) under nitrogen atmosphere was added potassium *t*-butoxide (0.57 g, 5.1 mmol). The mixture was stirred at room temperature for 24 h. Evaporation of the solvent gave a residue that was treated with water (25 mL) and then extracted with CH_2Cl_2 (2 x 35 mL). The organic layer was dried over sodium sulfate, the solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column with EtOAc. Subsequent crystallisation with diisopropyl ether gave 0.25 g, 27% of pure 2-oxo-4*H*-thieno[2,3-*f*][1,2,3]triazolo [1,5-*a*][1,4]oxazepine (**9**) as white amorphous powder having mp 69 °C. IR (Nujol): 1720 (cm^{-1}); ^{1}H-NMR: 5.12 (2H, s), 7.57 (1H, d, *J*=5.4), 7.66 (1H, d, *J*=5.4), 7.86 (1H, s); ^{13}C NMR: 54.5 (t), 127.2-130.1, 143.7 (s), 148.6 (s), 154.2 (s), 161.5 (s); MS: 207 *m/z* (M^+). *Anal.* Calcd for $C_8H_5N_3O_2S$: C, 46.37; H, 2.43; N, 20.29. Found: C, 46.42; H, 2.47; N, 20.35.

2-Hydroxycarbonyl-3-thenylazide (10). A solution of 2-methoxycabonyl-3-thenylazide (**3**) (1.57 g, 8.6 mmol) in dioxane (40 mL) and 2M aqueous sodium hydroxide (40 mL, 80.0 mmol) was stirred at room temperature for 2h. Hydrochloric acid was added to pH = 1 and the mixture was then extracted with EtOAc (3 x 30 mL). The organic layer was dried over sodium sulfate, the solvent was removed under reduced pressure and the residue was crystallised with MeOH giving 1.38 g, 95% of pure 2-hydroxy-carbonyl-3-thenylazide (**10**) having mp 108-109 °C. IR (Nujol): 3400, 2150 (cm^{-1}); ^{1}H-NMR: 7.00 (1H, d, *J*=5.3), 7.62 (1H, d, *J*=5.3), 8.40 (1H, br s); MS: 169 *m/z* (M^+). *Anal.* Calcd for $C_5H_3N_3O_2S$: C, 35.50; H, 1.79; N, 24.86. Found: C, 35.47; H, 1.81; N, 24.95.

2-(Propargylamino)carbonyl-3-thenylazide (11). A solution of 2-hydroxycarbonyl-3-thenylazide (**10**) (1.20 g, 7.1 mmol) in anhydrous toluene (50 mL) under nitrogen atmosphere was treated with thionyl chloride (1.01 g, 8.5 mmol) and then heated to 80 °C for 2 h. After cooling to room temperature, propargylamine (0.47 g, 8.5 mmol) was added and the mixture was stirred for 1 h. Water (25 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 30 mL). The organic layer was washed with 5% aqueous $NaHCO_3$ (15 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was crystallised with diisopropyl ether giving 0.95 g, 65% of pure

2-(propargylamino)carbonyl-3-thenylazide (**11**) having mp 98 °C. IR (Nujol): 3240, 2125, 1670 (cm^{-1}); ^{1}H-NMR: 2.30 (1H, t, *J*=2.5), 4.22 (2H, dd, *J*=5.3, 2.5), 6.97 (1H, d, *J*=5.4), 7.17 (br s), 7.49 (1H, d, *J*=5.4); MS: 206 *m/z* (M^+). *Anal.* Calcd for $C_8H_6N_4OS$: C, 46.60; H, 2.93; N, 27.19. Found: C, 46.63; H, 2.90; N, 27.23.

Intramolecular cycloaddition of 2-(propargylamino)carbonyl-3-thenylazide (11). A solution of (**11**) (0.80 g, 3.9 mmol) was refluxed in dry toluene (80 mL) under nitrogen atmosphere for 12 h. Evaporation of the solvent gave a residue that was chromatographed on a silica gel column with dichloromethane. Subsequent crystallisation with hexane-toluene gave 0.31 g, 39% of pure 2-oxo-4*H*-thieno[2,3-*f*][1,2,3] triazolo[1,5-*a*][1,4]diazepine (**8**).

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