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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

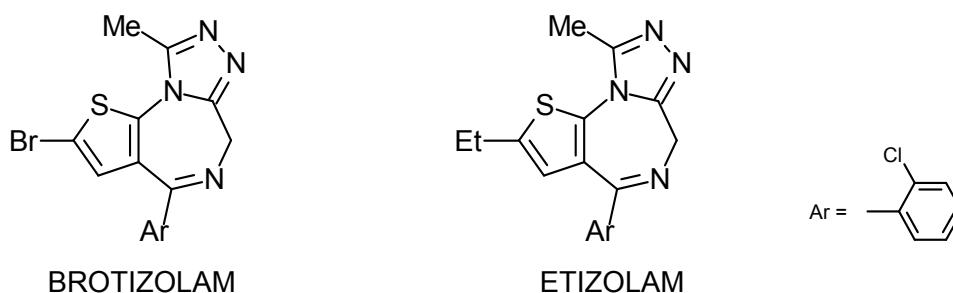
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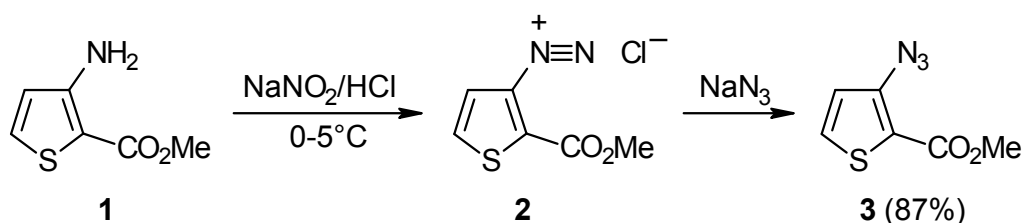
Abstract – Intermolecular dipolar cycloadditions between 2-methoxycarbonyl-3-thenylazide (**3**) and monosubstituted dipolarophiles bearing a triple carbon-carbon bond were exploited in a three step synthesis of the title compounds. The intramolecular cycloaddition of substituted thenylazide (**11**) 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 diazepines⁷ 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}



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).



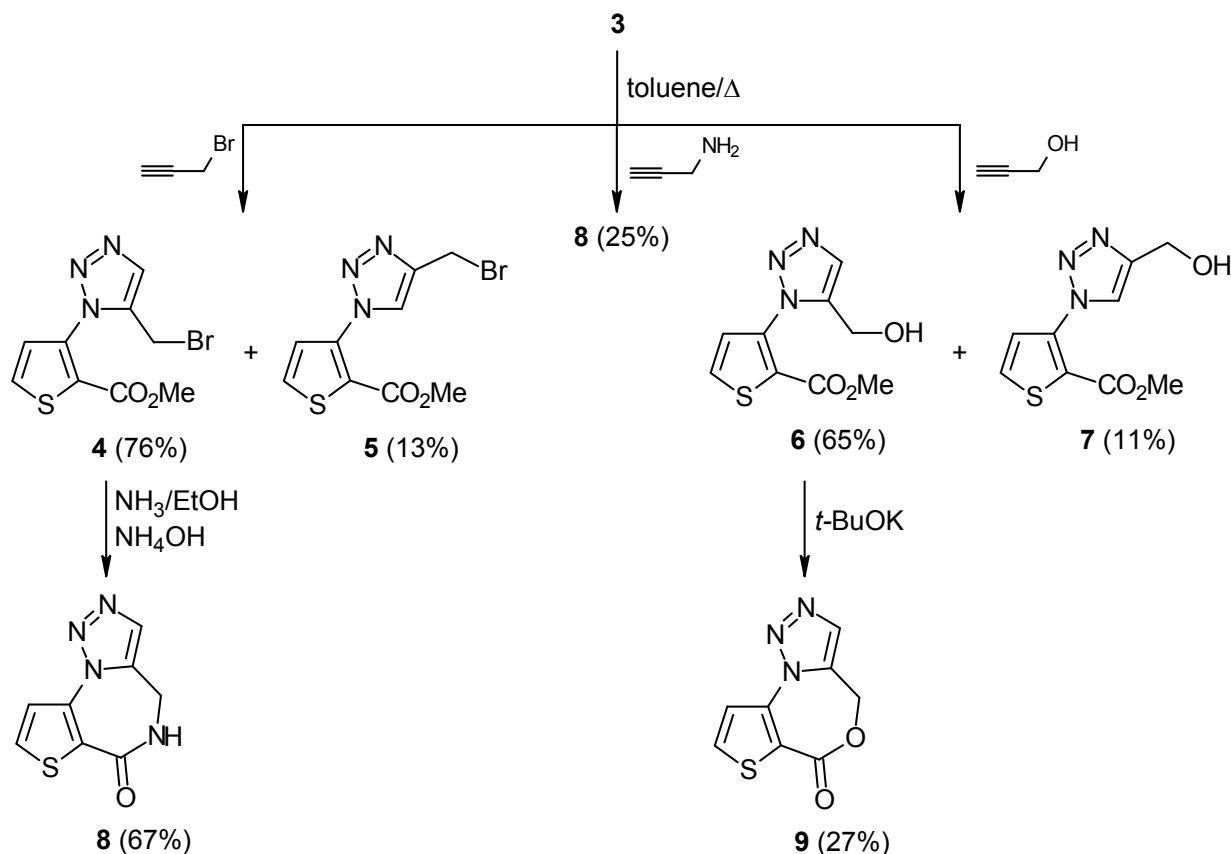
Scheme 1

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 ¹H and ¹³C 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.

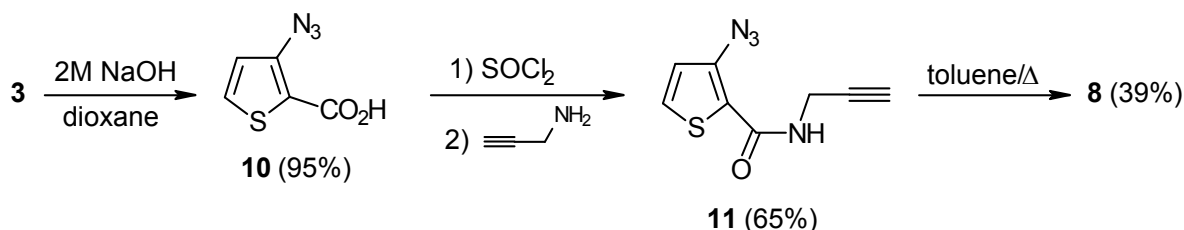
As the final step of our synthesis, the 1,4-diazepine ring closure of major cycloadducts (**4**) and (**6**) was carried out by internal nucleophilic attack. The required nucleophilic species were generated by treating (**4**) with ammonia and (**6**) with potassium *ter*-butoxide. No intermediates were 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**) $\rightarrow$ (**4**) $\rightarrow$ (**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**) $\rightarrow$ (**4**) $\rightarrow$ (**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. ¹H NMR (300 MHz) and ¹³C NMR (75 MHz) spectra were taken with a Bruker AMX 300 instrument (in CDCl₃ 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); ¹H-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 C₆H₅N₃O₂S: 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 CH₂Cl₂-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); ¹H-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); ¹³C 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 C₉H₈BrN₃O₂S:

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

Further elution gave 1-[(2-methoxycarbonyl)-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); ¹H-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); ¹³C 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 C₉H₈BrN₃O₂S: 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 CH₂Cl₂-EtOAc 10 : 1.

First fractions contained 1-[(2-methoxycarbonyl)-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); ¹H-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); ¹³C 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 C₉H₉N₃O₃S: C, 45.18; H, 3.79; N, 17.57. Found: C, 45.23; H, 3.82; N, 17.64.

Further elution gave 1-[(2-methoxycarbonyl)-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); ¹H-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); ¹³C 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 C₉H₉N₃O₃S: 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 CH₂Cl₂-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); ¹H-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); ¹³C 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 C₈H₆N₄OS: 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 NH₄OH (10 mL, 85.7 mmol) was stirred at room temperature for 48h. Evaporation of the solvent gave a residue that was extracted with CH₂Cl₂ (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 CH₂Cl₂ (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); ¹H-NMR: 5.12 (2H, s), 7.57 (1H, d, *J*=5.4), 7.66 (1H, d, *J*=5.4), 7.86 (1H, s); ¹³C 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 C₈H₅N₃O₂S: 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-methoxycarbonyl-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-hydroxycarbonyl-3-thenylazide (10) having mp 108-109 °C. IR (Nujol): 3400, 2150 (cm⁻¹); ¹H-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 C₅H₃N₃O₂S: 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 CH₂Cl₂ (3 x 30 mL). The organic layer was washed with 5% aqueous NaHCO₃ (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); ¹H-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 C₈H₆N₄OS: 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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