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A SHORT AND CONVENIENT SYNTHESIS OF NOVEL THIENOPYRAZOLODIAZEPINE AND THIENOPYRAZOLOXAZEPINE SKELETONS VIA NITRILIMINE CYCLOADDITION

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Abstract – Silver carbonate treatment of 3-thenyl-substituted hydrazonoyl chloride (**3**) promoted the *in situ* generation of the corresponding nitrilimine (**4**) which constitute the key intermediate in the three step synthesis of both thieno[2,3-*f*]pyrazolo[1,5-*a*][1,4]diazepine and thieno[2,3-*f*]pyrazolo[1,5-*a*][1,4]-oxazepine skeletons. The concurrent formation of unusual pyridazine derivatives arising from the electrophilic attack of a nitrilium cation to the carbon-carbon double bond is also discussed in some detail.

INTRODUCTION

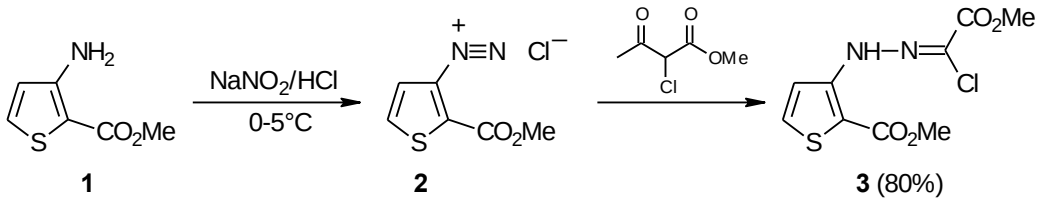
Since the early days of modern 1,3-dipolar cycloaddition chemistry, after the rationale introduced by Huisgen in the ‘60,[1] it becomes clear that nitrilimine cycloaddition represent a versatile and powerful tool in the construction of the pyrazole nucleus.[2] Then, the synthesis of annulated pyrazoles from both the inter-[3] and the intramolecular[4] cycloadditions of substituted nitrilimines disclosed the opportunity to obtain 4,5-dihydropyrazole derivatives of relevance in organic synthesis,[5] as well as some related products which received interesting biological applications.[6] For instance, benzodiazepines annulated to a nitrogen-containing five-membered ring like Alprazolam[7] and Estazolam[8] occupy a prominent place as drugs in the treatment of CNS disturbances. By replacing the benzenic ring of the benzodiazepine moiety with the thiophene one, thienotriazolodiazepine skeletons are obtained. Among these latter substrates Brotizolam[9] and Etizolam[10] belongs to a new class of diazepines which possesses amnesic, anxiolytic, anticonvulsant, hypnotic, sedative and skeletal muscle relaxant properties.

In the present paper we undertook the investigation of intermolecular cycloadditions between 3-thenyl-substituted hydrazonoyl chloride (**3**) and simple monosubstituted dipolarophiles bearing a

carbon-carbon double bond, namely allyl bromide and allyl alcohol, with the aim to synthesize the already unreported thieno[2,3-*f*]pyrazolo[1,5-*a*][1,4]diazepine and thieno[2,3-*f*]pyrazolo[1,5-*a*][1,4]-diazepine skeletons.

RESULTS AND DISCUSSION

Synthesis of thienopyrazolodiazepine and thienopyrazoloxazepine skeletons. 3-Thenyl-substituted hydrazonoyl chloride (**3**) was readily prepared from the commercially available aminoester (**1**) by diazotisation followed by coupling with ethyl 2-chloroacetoacetate (Scheme 1).



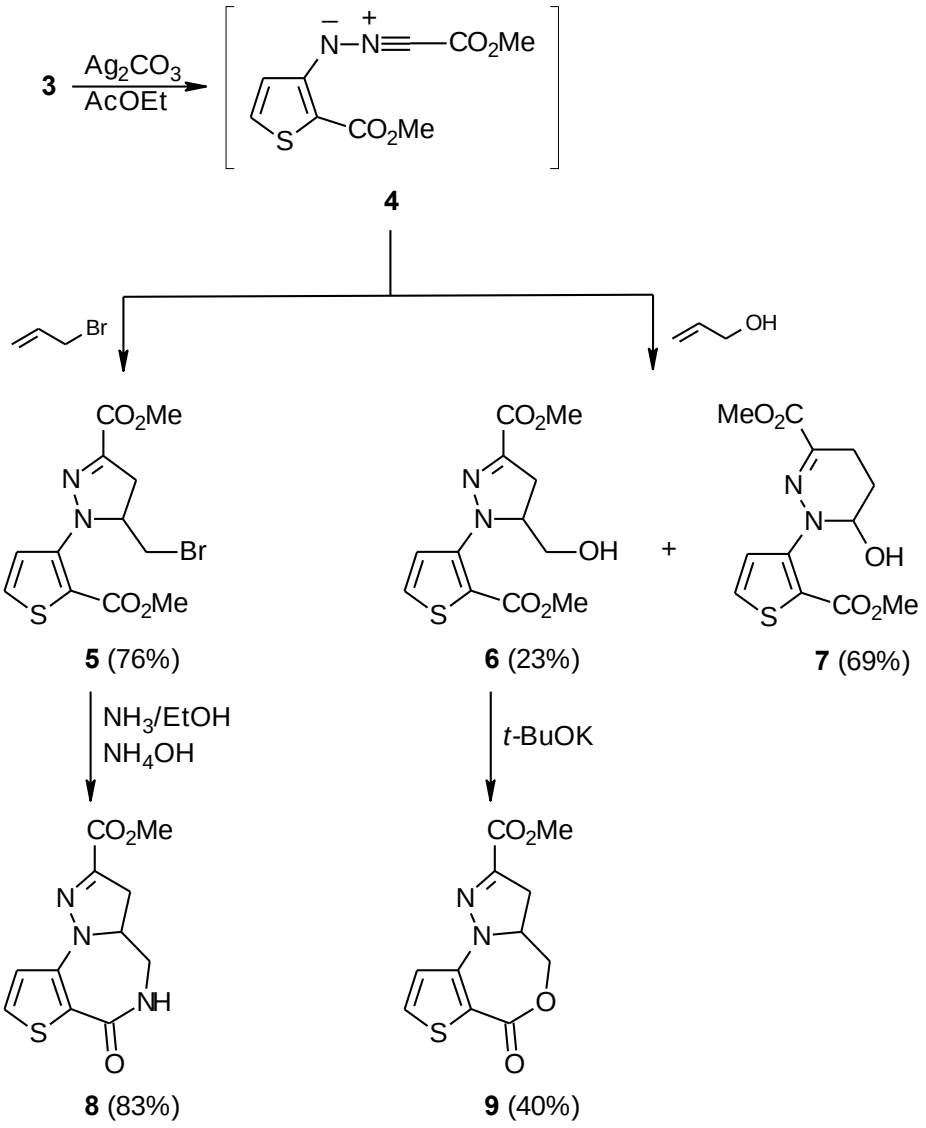
1 **2** **3** (80%)

Scheme 1

The *in situ* generation of the labile nitrilimine intermediate (**4**) was accomplished by treating the corresponding hydrazonoyl chloride (**3**) with a twofold molar excess of silver carbonate in ethyl acetate at room temperature following a well-established procedure previously elaborated by Garanti and Zecchi.[11] 4,5-Dihydropyrazoles (**5**), (**6**) and the 1,4,5,6-tetrahydropyridazine derivative (**7**) were obtained (see Scheme 2). The extent of the cycloaddition between hydrazonoyl chloride (**3**) and allyl bromide or allyl alcohol was strongly dependent upon the chemical features of the dipolarophile. While allyl bromide gave rise to the corresponding 4,5-dihydropyrazole (**5**) with 76% yield, allyl alcohol gave a mixture of the desired cycloadduct (**6**) (23%) and the unusual 1,4,5,6-tetrahydropyridazine derivative (**7**) (69%) (*vide infra*). The obtainment of 5-substituted-4,5-dihydropyrazoles (**5**) and (**6**) reflects the usual HOMO dipole control of nitrilimine cycloadditions to monosubstituted ethylenes.[12] In order to enhance the isolation yield of 4,5-dihydropyrazole (**6**), two other cycloaddition conditions were exploited. Unfortunately, the classic route carried out in the presence of a large excess of triethylamine in boiling toluene gave rise to large amounts of tarry materials, while non-classical aqueous conditions[13] performed in aqueous sodium hydrogencarbonate as the reaction medium in the presence of tetrahexylammonium chloride as the surfactant did not produce any appreciable result, since unreacted (**3**) was recovered.

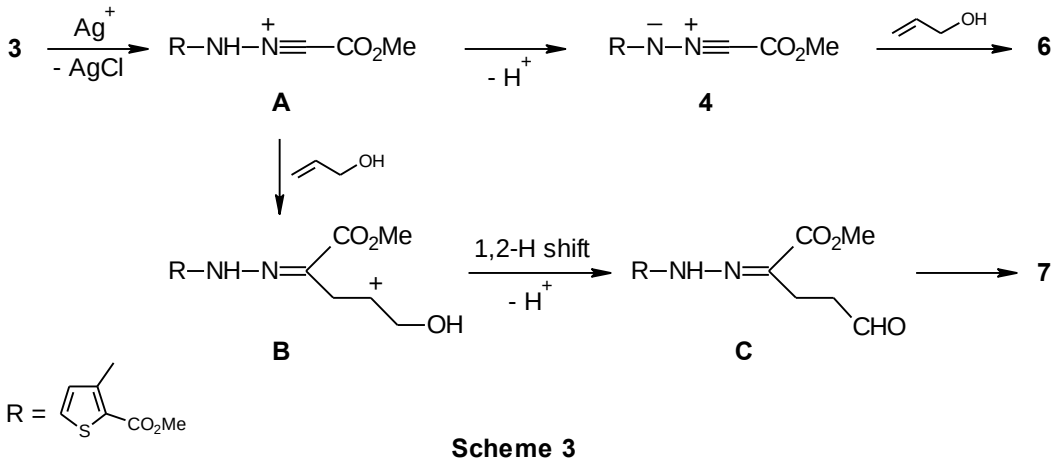
As the final step of our synthesis, the 1,4-diazepine or 1,4-oxazepine ring closure from cycloadducts (**5**) and (**6**), respectively, was carried out by internal nucleophilic attack. The required nucleophilic species were generated by treating (**5**) with ammonia and (**6**) with potassium *ter*-butoxide. 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 always recovered. The structure of all new compounds (**6**)-(**9**) were firmly established by elemental analyses and spectral data, including ^{1}H and ^{13}C-NMR, IR, and MS spectrometry (see Experimental section). In particular, ^{1}H-NMR spectra of target compounds (**8**) and (**9**) show a complex splitting pattern (overlapping signals) due to the four protons bonded to the pyrazoline and the 1,4-diazepine rings. Upon irradiation of the proton in the 5-position of the pyrazoline ring at 5.80 δ, two distinct AB systems appear in the case of compound (**8**). The first one at 3.29 δ (J = 18.2 Hz) is due to the two protons in the 3-position of the pyrazoline ring, while the second (3.34 δ, J = 12.1 Hz) is related to the couple of protons in the 3-position of the diazepine ring. These observed chemical shifts and scalar coupling constants are in perfect agreement to literature values.[14]



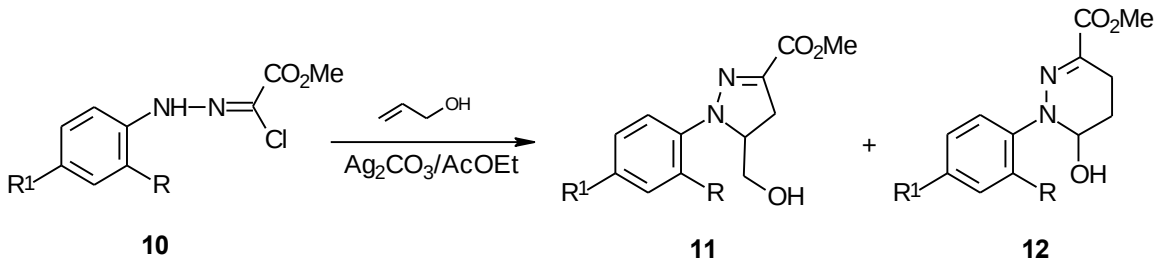
Scheme 2

Formation of 1,4,5,6-tetrahydropyridazine derivatives. To this point, we perceived the opportunity to study in some detail the formation of 1,4,5,6-tetrahydropyridazine derivatives quite similar to (**7**). Although unusual, the formation of the 1,4,5,6-tetrahydropyridazine ring from the reaction between hydrazonoyl chlorides and allyl alcohol is a documented matter[15] and can be rationalised on the grounds of the intermediates **A**-**C** depicted in the Scheme 3. Due to the ability of the silver ion to facilitate the heterolysis of the carbon-halogen bond,[16] it is reasonable to posit the initial formation of the nitrilium cation **A**. Further evolution of **A** lead to nitrilimine intermediate (**4**), which give cycloadduct (**6**), and to carbocation **B**. In the present case, pinacol-type rearrangement of the latter specie[17] give carbonyl derivatives **C** which cyclize to (**7**). It needs to be added that: (*i*) carbonyl derivatives quite similar to **C** were really isolated by reacting the 2-methoxycarbonylphenyl-substituted hydrazonoyl chloride (**10b** in the present paper) with but-3-en-2-ol and phenyl vinylcarbinol,[15] and (*ii*) the intermediacy of carbocation **B** as the precursor of both products (**6**) and (**7**) can be ruled out since the retention of stereochemistry in the case of substituted allylic alkenols.[15]



Scheme 3

Hence, hydrazonoyl chlorides (**10**) were submitted to reaction with allyl alcohol in the presence of silver carbonate (Scheme 4). Reaction output are summarised in Table 1 and show that product ratio (**12**) : (**11**) enhances according to the steric encumbrance of substituent R. This finding implies that the substituent R hinders the approach of nitrilimine (**4**) to the carbon-carbon double bond of allyl alcohol on parallel planes, as requested for the concerted mechanism of nitrilimine cycloadditions.[18] It is apparent that the presence of bulky R made easier the attack of nitrilium cation **A** to allyl alcohol with respect to that of nitrilimine (**4**). In fact, the approach of the electrophilic specie **A** to the carbon-carbon double bond does not suffer from the rigorous geometrical constraints which works in dipolar cycloadditions.



10 **11** **12**

Scheme 4

Table 1. Reaction between hydrazonoyl chlorides (**10**) and allyl alcohol.

R	R^1	Product yields (%)		Product ratio (**12**) : (**11**)
		(**11**)	(**12**)	
H	Me	93	—	0
CO_2Me	H	83	10	0.12
I	H	56	30	0.54
t-Bu	H	39	52	1.33

CONLUSIONS

The synthesis of the novel thieno[2,3-*f*]pyrazolo[1,5-*a*][1,4]diazepine and thieno[2,3-*f*]pyrazolo[1,5-*a*]-[1,4]oxazepine skeletons of potential interest as pharmacophoric agents have been carried out by the nitrilimine-alkene cycloaddition as the key step. Since the transformation (**5**) → (**8**) occur with 63% overall yield, the present synthetic approach constitutes a reliable way to obtain the above thienopyrazolodiazepine skeleton in the multi-gram scale. The occurrence of 1,4,5,6-tetrahydropyridazine as unusual products of the reaction between hydrazonoyl chlorides and allyl alcohol have been investigated by varying the size of the substituent R. An increase of the 1,4,5,6-tetrahydropyridazine yield was experienced in the presence of bulky R indicating the geometrical freedom of electrophilic attack by nitrilium cation **A** to the C=C bond with respect to concerted dipolar cycloaddition.

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.

Hydrazonoyl chlorides (**10a**),[19] (**10b**)[15] and 4,5-dihydropyrazole derivatives (**11a**),[20] (**11b**)[15] are known in the literature.

Synthesis of hydrazonoyl chlorides (3) and (10). General procedure. A solution of 2-methoxy-carbonyl-3-aminothiophene (**1**) or the appropriate aniline (15.0 mmol) in a mixture of water (25 mL) and MeOH (15 mL) was treated with aqueous HCl (10 M, 4.5 mL) and then cooled to 0 °C. Sodium nitrite (1.31 g, 19.0 mmol) was added portionwise to the cooled and stirred reaction mixture. After 15 min, the cold mixture was adjusted to pH 5 with sodium acetate and then a solution of methyl 2-chloroacetoacetate (2.34 g, 15.0 mmol) in MeOH (15 mL) was added with cooling and stirring of the mixture, which was stirred overnight at room temperature and then extracted with CH_2Cl_2 (2 x 35 mL). The organic layer was washed with aqueous sodium hydrogencarbonate (5%, 20 mL), dried over Na_2SO_4 and evaporated. Recrystallisation from *i*Pr_2O gave the pure hydrazonoyl chlorides (**3**) or (**10**).

Hydrazonoyl chloride (**3**) (3.31 g, 80%) as pale yellow powder having mp 163-165 °C; IR (Nujol): 3250, 1735, 1690 (cm^{-1}); ^{1}H-NMR: 3.95 (3H, s), 3.97 (3H, s), 7.38 (1H, d, *J* = 5.4), 7.47 (1H, d, *J* = 5.4), 10.80 (1H, br s). MS: 276 *m/z* (M^+). *Anal*. Calcd for $C_9H_9ClN_2O_4S$: C, 39.06; H, 3.28; N, 10.13. Found: C, 39.10, H, 3.31; N, 10.19.

Hydrazonoyl chloride (**10c**) (4.36 g, 86%) as yellow powder having mp 95-97 °C; IR (Nujol): 3270, 1735 (cm^{-1}); ^{1}H-NMR: 3.98 (3H, s), 6.84 (1H, td, *J* = 7.5, 1.6), 7.38 (1H, td, *J* = 7.5, 1.6), 7.60 (1H, dd, *J* = 8.4, 2.2), 7.76 (1H, dd, *J* = 8.4, 2.2), 8.81 (1H, br s). MS: 338 *m/z* (M^+). *Anal*. Calcd for $C_9H_8ClIN_2O_2$: C, 31.91; H, 2.38; N, 8.28. Found: C, 31.96, H, 2.42; N, 8.33.

Hydrazonoyl chloride (**10d**) (3.62 g, 90%) as white powder having mp 67-69 °C; IR (Nujol): 3240, 1730 (cm^{-1}); ^{1}H-NMR: 0.94 (9H, s), 3.95 (3H, s), 6.89 (1H, td, *J* = 7.4, 1.8), 7.30 (1H, td, *J* = 7.4, 1.8), 7.51 (1H, dd, *J* = 8.5, 2.1), 7.70 (1H, dd, *J* = 8.5, 2.1), 8.80 (1H, br s). MS: 268 *m/z* (M^+). *Anal*. Calcd for $C_{13}H_{17}ClN_2O_2$: C, 58.08; H, 6.38; N, 10.43. Found: C, 58.11, H, 6.41; N, 10.50.

Cycloaddition between hydrazonoyl chloride (3) and allyl bromide.

A solution of hydrazonoyl chloride (**3**) (2.50 g, 9.1 mmol) and allyl bromide (3.30 g, 27.3 mmol) in EtOAc (45 mL) was treated with silver carbonate (5.02 g, 18.2 mmol), and stirred in the dark at room temperature for 48 h. The undissolved material was filtered off, the solvent was evaporated, and then the residue was chromatographed on a silica gel column with hexane-EtOAc 7 : 3 giving 1-[(2-metoxy-carbonyl)-3-thenyl]-3-methoxycarbonyl-5-bromomethyl-4,5-dihydropyrazole (**5**) (2.50 g, 76% yield) as pale yellow powder having mp 152-154 °C (from *i*Pr_2O); IR (Nujol): 1715, 1700 (cm^{-1}); ^{1}H-NMR: 3.22-3.46 (4H, m), 3.89 (3H, s), 3.92 (3H, s), 5.80-5.90 (1H, m), 7.37 (1H, d, *J* = 5.4), 7.44 (1H, d, *J* = 5.4). After irradiation at 5.85 δ: 3.27 (1H, d, *J* = 18.1), 3.29 (1H, d, *J* = 11.0), 3.34 (1H, d, *J* = 18.1), 3.42 (1H, d, *J* = 11.0). ^{13}C-NMR: 33.2 (t), 37.2 (t), 52.0 (q), 52.3 (q), 62.5 (d), 125.0 (d), 130.7 (d), 133.6 (s), 141.1 (s), 145.6 (s), 161.6 (s), 162.5 (s). MS: 361 *m/z* (M^+). *Anal*. Calcd for $C_{12}H_{13}BrN_2O_4S$: C, 39.89; H, 3.63; N, 7.76. Found: C, 39.93, H, 3.67; N, 7.82.

Cycloaddition between hydrazonoyl chloride (3) and allyl alcohol.

A solution of the hydrazonoyl chloride (**3**) (2.48 g, 9.0 mmol) and allyl alcohol (2.61 g, 45.0 mmol) in EtOAc (40 mL) was treated with silver carbonate (4.97 g, 18.0 mmol), and stirred in the dark at room temperature for 64 h. The undissolved material was filtered off, the solvent was evaporated, and then the residue was chromatographed on a silica gel column with hexane-EtOAc 10 : 3. First fractions contained 1-[(2-methoxycarbonyl)-3-thenyl]-3-methoxycarbonyl-6-hydroxy-1,4,5,6-tetrahydropyridazine (**7**) (1.85 g, 69% yield) as yellow powder having mp 120-122 °C (from *i*Pr_2O); IR (Nujol): 3450, 1720, 1690 (cm^{-1}); ^{1}H-NMR: 1.25-1.55 (1H, m), 2.14-2.21 (1H, m), 2.54-2.79 (2H, m), 3.84 (3H, s), 3.88 (3H, s), 5.32 (1H, dd, *J* = 8.4, 2.7), 5.60 (1H, br s), 7.11 (1H, d, *J* = 5.4), 7.39 (1H, d, *J* = 5.4). After addition of D_2O: 1.52 (1H, dddd, *J* = 9.8, 7.2, 6.2, 2.5), 2.14-2.21 (1H, m), 2.62 (1H, ddd, *J* = 18.4, 13.8, 6.6), 2.77 (1H, ddd, *J* = 18.4, 8.5, 6.0). ^{13}C-NMR: 16.3 (t), 22.3 (t), 52.3 (q), 52.5 (q), 78.8 (d), 126.2 (d), 131.1 (d), 133.5 (s), 138.4 (s), 145.8 (s), 160.4 (s), 162.8 (s). MS: 298 *m/z* (M^+). *Anal*. Calcd for $C_{12}H_{14}N_2O_5S$: C, 48.31; H, 4.73; N, 9.40. Found: C, 48.27, H, 4.69; N, 9.44.

Further elution with EtOAc gave 1-[(2-metoxycarbonyl)-3-thenyl]-3-methoxycarbonyl-5-hydroxymethyl-4,5-dihydropyrazole (**6**) (0.62 g, 23% yield) as white powder having mp 132-134 °C (from *i*Pr_2O); IR (Nujol): 3500, 1720, 1710 (cm^{-1}); ^{1}H-NMR: 3.65-3.70 (2H, m), 3.71 (1H, dd, *J* = 8.6, 2.0), 3.79 (1H, dd, *J* = 8.6, 1.8) 3.80 (3H, s), 3.82 (3H, s), 4.84 (1H, br s), 5.23-5.31 (1H, m), 7.26 (1H, d, *J* = 5.4), 7.43 (1H, d, *J* = 5.4). ^{13}C-NMR: 34.7 (t), 52.1 (q), 52.2 (q), 61.9 (t), 65.2 (d), 125.0 (d), 130.8 (d), 133.6 (s), 140.3 (s), 144.7 (s), 160.8 (s), 162.2 (s). MS: 298 *m/z* (M^+). *Anal*. Calcd for $C_{12}H_{14}N_2O_5S$: C, 48.31; H, 4.73; N, 9.40. Found: C, 48.36, H, 4.77; N, 9.46.

Cyclisation to thieno[2,3-*f*]pyrazolo[1,5-*a*][1,4]diazepine (8).

A solution of (**5**) (1.44 g, 4.0 mmol) in 2M ethanolic ammonia (40 mL, 80.0 mmol) and 30% aqueous ammonium hydroxide (10 mL, 85.7 mmol) was stirred at room temperature for 48 h. Partial evaporation of the solvent gave a residue that was extracted with CH_2Cl_2 (70 mL). The organic layer was dried over Na_2SO_4, the solvent was removed under reduced pressure and the residue was crystallised with *i*Pr_2O giving pure 2-oxo-6-methoxycarbonyl-4*H*-thieno[2,3-*f*]pyrazolo[1,5-*a*][1,4]diazepine (**8**) (0.88 g, 83% yield) as white powder having mp 163-165 °C; IR (Nujol): 3430, 1730, 1690 (cm^{-1}); ^{1}H-NMR: 3.22-3.41 (4H, m), 3.85 (3H, s), 5.75-5.85 (1H, m), 7.16 (1H, d, *J* = 5.4), 7.28 (1H, br s), 7.40 (1H, d, *J* = 5.4). After irradiation at 5.80 δ: 3.26 (1H, d, *J* = 18.2), 3.30 (1H, d, *J* = 12.1), 3.32 (1H, d, *J* = 18.2), 3.38 (1H, d, *J* = 12.1). ^{13}C-NMR: 36.5 (t), 52.0 (q), 60.8 (t), 62.5 (d), 124.7 (d), 130.9 (d), 137.2 (s), 144.5 (s), 145.9 (s), 161.6 (s), 163.6 (s). MS: 265 *m/z* (M^+). *Anal*. Calcd for $C_{11}H_{11}N_3O_3S$: C, 49.80; H, 4.18; N, 15.85. Found: C, 49.75, H, 4.21; N, 15.92.

Cyclisation to thieno[2,3-*f*]pyrazolo[1,5-*a*][1,4]oxazepine (9).

To a solution of (**6**) (1.31 g, 4.4 mmol) in anhydrous tetrahydrofuran (30 mL) under nitrogen atmosphere was added potassium *ter*-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 taken up with water (25 mL) and then extracted with CH_2Cl_2 (2 x 35 mL). The organic layer was dried over Na_2SO_4, the solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column with EtOAc. Subsequent crystallisation with *i*Pr_2O gave pure 2-oxo-6-methoxycarbonyl-4*H*-thieno[2,3-*f*]pyrazolo[1,5-*a*][1,4]-oxazepine (**9**) (0.47 g, 40%) as a white powder having mp 229-231 °C; IR (Nujol): 1720, 1690 (cm^{-1}); ^{1}H-NMR: 3.02 (1H, dd, *J* = 18.5, 10.8), 3.60 (1H, dd, *J* = 18.5, 12.8), 3.94 (3H, s), 4.49 (2H, m), 4.63-4.70 (1H, m), 7.32 (1H, d, *J* = 5.4), 7.62 (1H, d, *J* = 5.4). ^{13}C-NMR: 34.1 (t), 52.6 (q), 63.1 (t), 68.6 (d), 120.2 (d), 128.8 (d), 130.8 (s), 135.4 (s), 143.1 (s), 160.8 (s), 162.4 (s). MS: 266 *m/z* (M^+). *Anal*. Calcd for $C_{11}H_{10}N_2O_4S$: C, 49.62; H, 3.79; N, 10.53. Found: C, 49.58, H, 3.76; N, 10.59.

Cycloaddition between hydrazonoyl chlorides (10) and allyl alcohol. General procedure.

A solution of the hydrazonoyl chloride (**10**) (8.0 mmol) and allyl alcohol (2.32 g, 40.0 mmol) in EtOAc (40 mL) was treated with silver carbonate (4.41 g, 16.0 mmol), and stirred in the dark at room temperature for 60 h. The undissolved material was filtered off, the solvent was evaporated, and then the residue was chromatographed on a silica gel column with CH_2Cl_2-EtOAc 8 : 2. First fractions contained tetrahydropyridazine derivatives (**12**), further elution gave dihydropyrazoles (**11**).

Dihydropyrazole (**11c**) (1.61 g, 56%) as pale yellow powder having mp 131-132 °C (from *i*Pr_2O); IR (Nujol): 3450, 1730 (cm^{-1}); ^{1}H-NMR: 3.22 (1H, dd, *J* = 17.7, 8.8), 3.29 (1H, dd, *J* = 17.7, 10.9), 3.43 (1H, dd, *J* = 11.9, 3.3), 3.47 (1H, dd, *J* = 11.9, 4.3), 3.83 (3H, s), 4.67 (1H, br s), 4.77-4.86 (1H, m), 6.95 (1H, td, *J* = 7.6, 1.8), 7.31-7.34 (2H, m), 7.84 (1H, dd, *J* = 8.6, 2.1). ^{13}C-NMR: 34.1 (t), 52.1 (q), 61.5 (t), 66.6 (d), 126.7 (d), 128.0 (d), 129.0 (d), 139.5 (d), 140.0 (s), 142.0 (s), 145.4 (s), 163.0 (s). MS: 360 *m/z* (M^+). *Anal*. Calcd for $C_{12}H_{13}IN_2O_3$: C, 40.00; H, 3.64; N, 7.78. Found: C, 40.05; H, 3.68; N, 7.84.

Dihydropyrazole (**11d**) (0.90 g, 39%) as white powder having mp 100-102 °C (from *i*pr_2O); IR (Nujol): 3400, 1720 (cm^{-1}); ^{1}H-NMR: 0.94 (9H, s), 3.25 (1H, dd, *J* = 17.8, 8.5), 3.30 (1H, dd, *J* = 17.8, 11.2), 3.45 (1H, dd, *J* = 12.0, 3.5), 3.51 (1H, dd, *J* = 12.0, 4.8), 3.81 (3H, s), 4.70 (1H, br s), 4.75-4.84 (1H, m), 6.87 (1H, td, *J* = 7.5, 1.7), 7.20-7.30 (2H, m), 7.61 (1H, dd, *J* = 8.5, 2.5). ^{13}C-NMR: 21.1 (s), 28.7 (q), 34.8 (t), 52.6 (q), 63.5 (t), 68.1 (d), 125.4 (d), 127.2 (d), 129.8 (d), 137.7 (d), 139.4 (s), 140.9 (s), 146.8 (s), 162.6 (s). MS: 290 *m/z* (M^+). *Anal*. Calcd for $C_{16}H_{22}N_2O_3$: C, 66.17; H, 7.64; N, 9.65. Found: C, 66.22; H, 7.61; N, 9.71.

Tetrahydropyridazine (**12b**) (0.23 g, 10%) as white powder having mp 100-103 °C (from *i*Pr_2O); IR (Nujol): 3400, 1730, 1710 (cm^{-1}); ^{1}H-NMR: 2.21-2.87 (4H, m), 3.83 (3H, s), 3.89 (3H, s), 5.37 (1H, dd, *J*

= 8.4, 4.7), 5.60 (1H, br s), 7.15-8.02 (4H, m). ^{13}C-NMR: 21.7 (t), 23.9 (t), 51.4 (q), 53.2 (q), 97.6 (d), 127.2 (d), 129.0 (d), 130.7 (d), 131.8 (d), 133.9 (s), 141.9 (s), 147.9 (s), 163.4 (s), 165.9 (s). MS: 292 *m/z* (M^+). *Anal*. Calcd for $C_{14}H_{16}N_2O_5$: C, 57.51; H, 5.52; N, 9.59. Found: C, 57.47; H, 5.49; N, 9.62.

Tetrahydropyridazine (**12c**) (0.86 g, 30%) as pale yellow powder having mp 140-142 °C (from *i*Pr_2O); IR (Nujol): 3400, 1720 (cm^{-1}); ^{1}H-NMR: 2.17-2.76 (4H, m), 3.87 (3H, s), 4.93 (1H, dd, *J* = 8.0, 2.5), 5.31 (1H, br s), 6.90-7.90 (4H, m). ^{13}C-NMR: 20.9 (t), 23.5 (t), 52.5 (q), 98.9 (d), 126.4 (d), 128.6 (d), 129.4 (d), 130.3 (d), 132.0 (s), 140.0 (s), 147.4 (s), 165.2 (s). MS: 360 *m/z* (M^+). *Anal*. Calcd for $C_{12}H_{13}IN_2O_3$: C, 40.00; H, 3.64; N, 7.78. Found: C, 39.95; H, 3.70; N, 7.84.

Tetrahydropyridazine (**12d**) (1.21 g, 52%) as white powder having mp 96-98 °C (from *i*Pr_2O); IR (Nujol): 3450, 1720 (cm^{-1}); ^{1}H-NMR: 0.91 (9H, s), 2.11-2.68 (4H, m), 3.85 (3H, s), 5.04 (1H, dd, *J* = 8.2, 3.7), 5.50 (1H, br s), 6.90-7.60 (4H, m). ^{13}C-NMR δ 20.9 (s), 21.3 (t), 25.2 (t), 27.6 (q), 51.8 (q), 95.6 (d), 125.0 (d), 127.2 (d), 129.0 (d), 131.7 (d), 133.6 (s), 141.4 (s), 146.5 (s), 163.8 (s). MS: 290 *m/z* (M^+). *Anal*. Calcd for $C_{16}H_{22}N_2O_3$: C, 66.17; H, 7.64; N, 9.65. Found: C, 66.21; H, 7.60; N, 9.72.

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