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INTRAMOLECULAR NITRILIMINE CYCLOADDITIONS TO THE THIOPHENE AND THE FURAN RINGS

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Abstract – The dipolarophilic behaviour of furan and thiophene rings have been exploited in the intramolecular cycloadditions of nitrilimines. These labile intermediates were generated from the corresponding hydrazonoyl chlorides by treatment with silver carbonate. The extent of formation of tricyclic cycloadducts was strongly dependent on the substitution pattern of the heteroaromatic ring, thus reflecting the HOMO-dipole controlled nature of the cycloaddition.

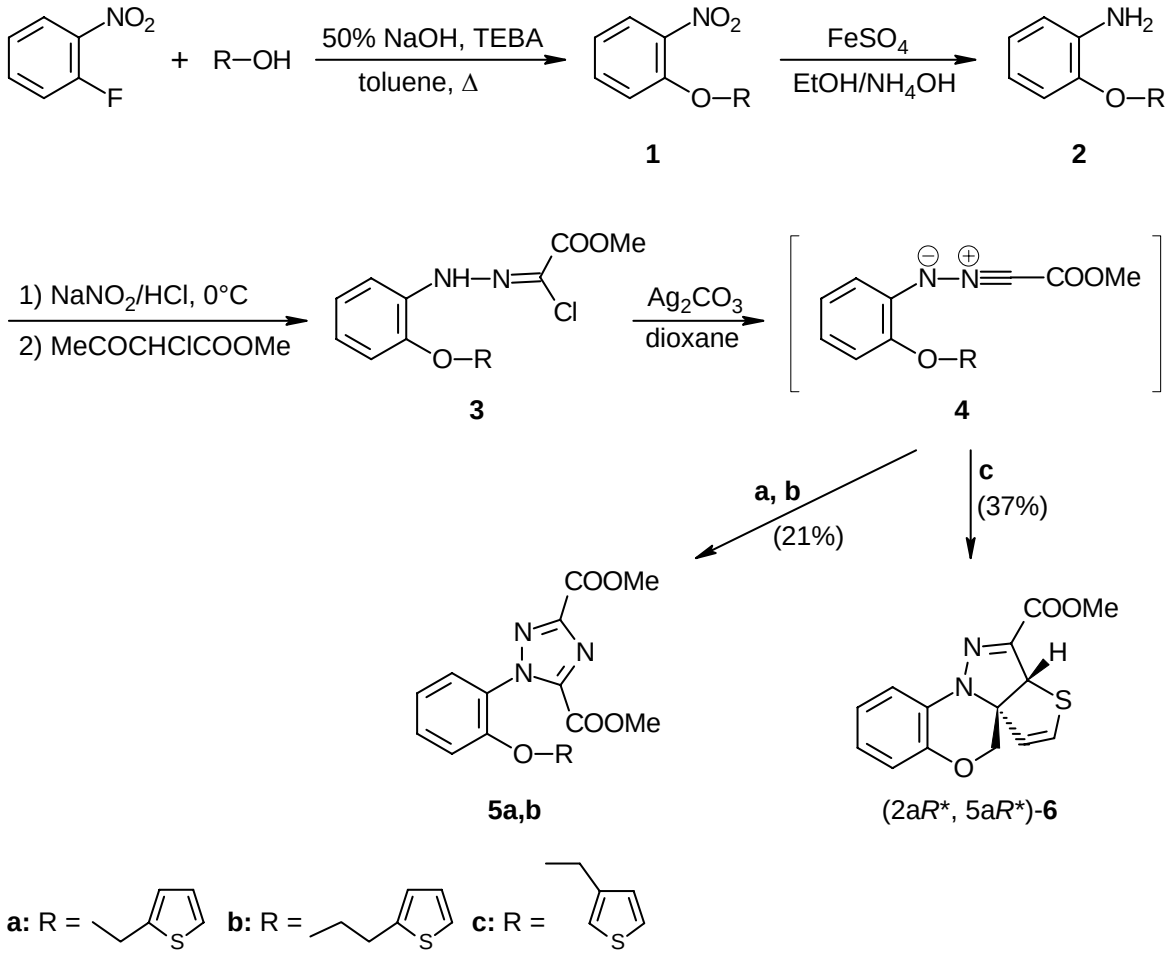
INTRODUCTION

In recent times, intramolecular 1,3-dipolar cycloadditions of nitrilimines have been exploited as the key step of synthetic routes leading to complex policyclic as well as strained heterocycles.[1-3] Various five-membered heteroaromatics were found to behave as efficient dipolarophiles in these reactions providing interesting, strained tricyclic pyrazolines.[4] Although some relevant studies involved the furan[5] and the thiophene[6] rings, all the published papers are concerned with the reaction of *C*-substituted nitrilimines, while no data are available on the behaviour of *N*-substituted nitrilimines. To fill this gap, we have undertaken the present investigation, dealing with the reactions of appropriately substituted nitrilimines (**4**) containing the thiophene moiety and the furyl- substituted analogues (**9**).

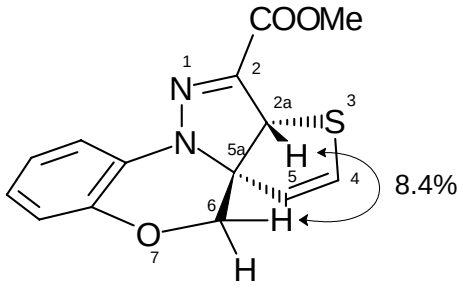
RESULTS AND DISCUSSION

2-Nitrophenyl-(thenyl)alkyl ethers (**1**) were first submitted to reduction to the corresponding amino derivatives (**2**) (Scheme 1). Diazotization of the latter followed by treatment with methyl 2-chloroaceto acetate gave hydrazonoyl chlorides (**3**), which were reacted in dry dioxane at room temperature by using four mole equivalents of silver carbonate. Structural assignement of products (**5**) and (**6**) relied upon analytical and spectral data. Proton NMR spectroscopy was particularly useful in the elucidation of

structure (**6**). In particular, the hydrogens in the 6- position of this tetracyclic cycloadduct (see Figure 1) appears as an AB system at δ 4.10 (d, *J* = 11.8 Hz), and 4.66 (d, *J* = 11.8 Hz), while the proton in the 2a- position appears as a singlet at δ 4.80. Moreover, the relative configurations of the two newly-formed stereocentres of (**6**) were established by mutual NOE enhancement which showed that the proton in the 2a- position lies neighbouring to that in the 6- position. It is apparent that this NOE effect can only be operative in the case of the stereochemical arrangement depicted in Figure 1.



Scheme 1



(2a*R**, 5a*R**)-**6**

Figure 1. Mutual NOE enhancements of tetracyclic cycloadducts (2a*R**,5a*R**)-(**6**).

The results depicted in Scheme 1 deserve some comments in order to rationalise the observed reaction paths. It is apparent that both geometric constraints and electronic factors must be responsible for the regiochemical trend of the cycloaddition. In fact, experimental results dealing with nitrilimine cycloadditions to thiophene[6] have shown that the preferred orientation involves bond formation between the carbon of the dipole and the α-carbon of the heterocycle according to the HOMO-dipole controlled nature of this processes. This explains the formation of (**6**) as well as the lack of intramolecular cycloaddition products arising from nitrilimines (**4a,b**) which should give extremely strained and bridged cycloadducts. In the latter case, some quantity of 1,2,4-triazole by-products (**5a,b**) arising from the cycloaddition between the nitrilimine intermediate and methyl cyanoformiate were recovered. It is well known that this latter dipolarophilic fragment originates from the decomposition of the nitrilimine itself.[7]
In order to gain some insight into the intramolecular cycloaddition to the thiophene ring of (**4c**), we undertook a B3LYP/cc-pVDZ computational investigation. First, we computed the minimum energy structures of the nitrilimine (**4c**), of the tetracyclic cycloadduct (**6**) and of the corresponding transition state (**TS6**). The reaction energy resulted ΔE_r = -40.2 kcal/mol, while the activation energy was $\Delta E^{\ddagger}$ = 18.1 kcal/mol. Transition state (**TS6**), which was confirmed by harmonic analysis, is consistent with a concerted mechanism and is only slightly asynchronous. In fact, the length of the forming bonds are 2.450 and 2.323 Å for the C–N and C–C bonds, respectively.

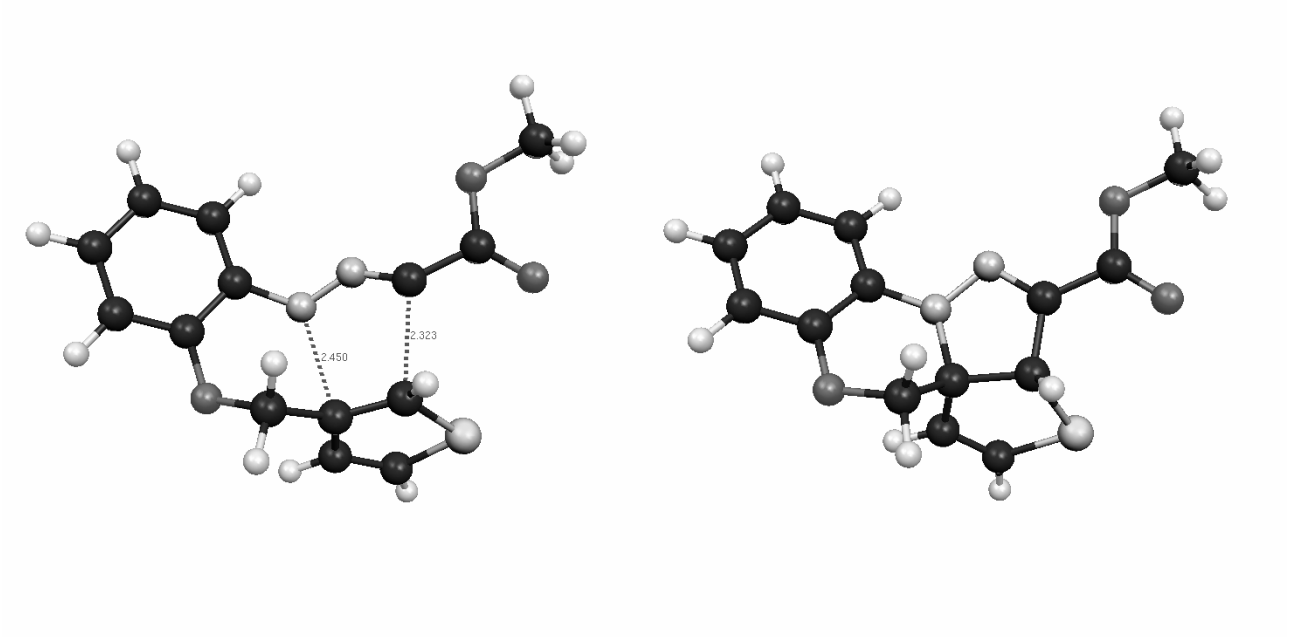
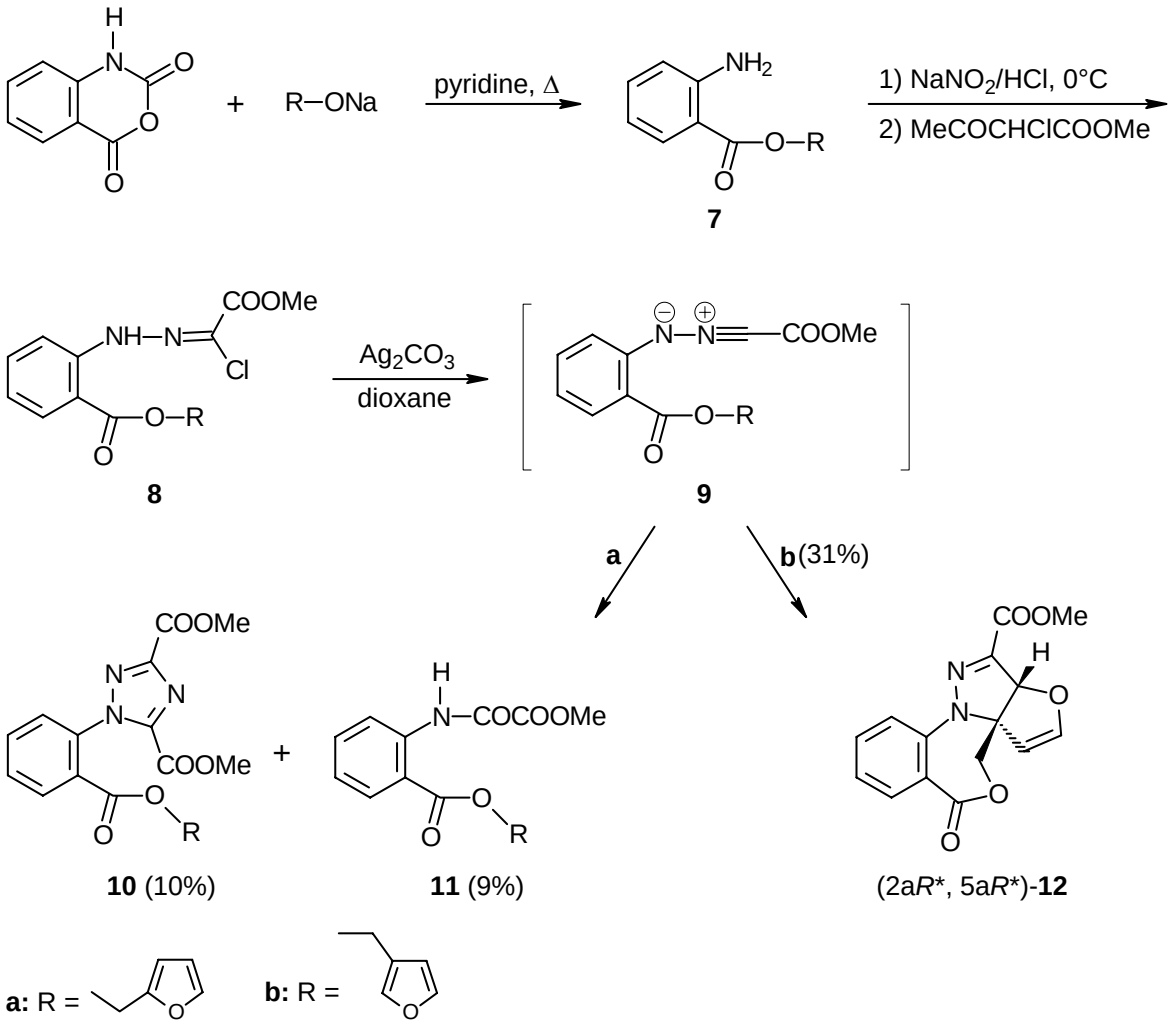


Figure 2. Structure of the transition state (**TS6**) (left) and of the energy minimum structure of (**6**) (right) optimized at the B3LYP/cc-pVDZ level. The distances relevant on (**TS6**) are 2.450 and 2.323 Å for the C-N and C-C bonds, respectively.

As a further step of our work, we studied the behaviour of the furan ring as dipolarophile in the intramolecular cycloadditions of nitrilimines (**9a,b**) (Scheme 2). Their precursors, namely hydrazonoyl chlorides (**8a,b**), were easily synthesised in two passages from isatoic anhydride. Treatment of (**8a,b**) with silver carbonate gave the tetracycle (2a*R**,5a*R**)-(**12**) in the case of 3-furyl substituted (**8b**), while the 2-furyl isomer (**8a**) gave by-products arising from the decomposition of the corresponding nitrilimine.[8] This behaviour just matches that observed in the case of thenyl-substituted nitrilimines (**4**). Here again, the relative configurations of the two newly-formed stereocentres of (2a*R**,5a*R**)-(**12**) were established by a 12.5% NOE enhancement between the proton in the 2a- position and that of the oxazepine ring.



Scheme 2

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) 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.

Compounds (**1a**),[9] (**1c**),[9] (**2a**),[9] (**2c**)[9] and (**7a**)[10] are known in the literature.

2-Nitrophenyl-2-(2-thenyl)ethyl ether (1b). A mixture of 2-nitrofluorobenzene (4.10 g, 29.0 mmol), 2-hydroxyethylthiophene (3.71 g, 29.0 mmol), benzyltriethylammonium chloride (0.34 g, 1.5 mmol) and aqueous 50% NaOH (8.9 g) in anhydrous toluene (100 mL) was stirred at rt for 4 h. The mixture was washed with water (150 mL), and the organic layer was dried over sodium sulfate. The solvent was removed under reduced pressure giving 6.93 g (96%) of 2-nitrophenyl 2-(2-thenyl)ethyl ether (**1b**) as colourless oil; IR (Nujol): 1535 (cm^{-1}); ^{1}H-NMR: 3.30 (2H, t, *J* = 6.7, -C<u>H</u>$_2$CH$_2$-), 4.22 (2H, t, *J* = 6.7, -C<u>H</u>$_2$CH$_2$-), 6.8-7.8 (7H, m, aromatics); MS: 249 *m/z* (M^+). *Anal.* Calcd for $C_{12}H_{11}NO_3S$: C, 57.82; H, 4.45; N, 5.62. Found: C, 57.88; H, 4.50; N, 5.69.

2-Aminophenyl 2-(2-thenyl)ethyl ether (2b). A solution of iron (II) sulfate heptahydrate (30.0 g, 0.11 mol) in water (45 mL) and EtOH (18.0 mL) was warmed to 90°C. A solution of (**1b**) (3.0 g, 12.0 mmol) in EtOH (18 mL) and a solution of 30% NH_4OH (54 mL) were added dropwise at the same time. The resulting solution was refluxed for 1h, then it was partially evaporated under reduced pressure. The mixture was extracted with Et_2O (3 x 50 mL) and the organic layer was dried over sodium sulfate. Evaporation under reduced pressure afforded 1.71 g (65%) of 2-aminophenyl 2-(2-thenyl)ethyl ether (**2b**) as colourless oil; IR (Nujol): 3470, 3370 (cm^{-1}); ^{1}H-NMR: 3.35 (2H, t, *J* = 6.7, -C<u>H</u>$_2$CH$_2$-), 3.80 (2H, br s, -N<u>H</u>$_2$), 4.25 (2H, t, *J* = 6.7, -C<u>H</u>$_2$CH$_2$-), 6.6-7.3 (7H, m, aromatics); MS: 219 *m/z* (M^+). *Anal.* Calcd for $C_{12}H_{13}NOS$: C, 65.72; H, 5.97; N, 6.39. Found: C, 65.77; H, 6.01; N, 6.46.

(3-Furyl)methyl anthranilate (7b). Sodium hydride (0.92 g, 38.3 mmol) was slowly added to a solution of 3-hydroxymethylfurane (3.00 g, 30.6 mmol) in dry toluene (60 mL) at rt. The solution was refluxed under nitrogen for 45 min, then isatoic anhydride (5.00 g, 30.6 mmol) in pyridine (60 mL) was added portionwise. The mixture was refluxed for 5 h, poured onto water-ice (120 mL) and extracted with Et_2O. The organic layer was washed with water (5 x 25 mL), dried over sodium sulfate and evaporated under reduced pressure giving 2.66 g (40%) of (3-furyl)methylanthranilate as pale yellow oil; IR (Nujol): 3490, 3380, 1690 (cm^{-1}); ^{1}H-NMR: 5.30 (2H, s, -C<u>H</u>$_2$O-), 5.65 (2H, br s, -N<u>H</u>$_2$), 6.6-7.8 (7H, m, aromatics); MS: 217 *m/z* (M^+). *Anal.* Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.30; H, 5.13; N, 6.51.

Hydrazonoyl chlorides (3) and (8). A solution of (**2**) or (**7**) (4.0 mmol), 37% aqueous HCl (2.2 mL) and AcOH (7.0 mL) in water (6.5 mL) was cooled to 0°C. Sodium nitrite (0.38 g, 5.5 mmol) was added portionwise under vigorous stirring and ice-cooling. After 10 min the pH was adjusted to 5 with NaOAc (2.05 g, 25.0 mmol) and methyl 2-chloroacetoacetate (0.60 g, 4.0 mmol) in MeOH (3.5 mL) was added. The mixture was kept to 0°C for 2 h, then at rt for 16 h. Et_2O (50 mL) was added and the organic layer was washed first with 5% aqueous $NaHCO_3$ (25 mL), then with water (50 mL), and dried over sodium sulfate. Evaporation of the solvent under reduced pressure gave crude hydrazonoyl chlorides which were cristallised from diisopropyl ether affording pure (**3**) or (**7**).

1-(2-Thenyl)oxymethyl-2-[2-(1-chloro-2-methoxy-2-oxoethylidene)hydrazino]benzene (**3a**) (0.83 g, 64%) as white needles having mp 97°C; IR (Nujol): 3320, 1720 (cm^{-1}); ^{1}H-NMR: 3.88 (3H, s, C<u>H</u>$_3$OOC-), 5.28 (2H, s, -C<u>H</u>$_2$O-), 6.9-7.6 (7H, m, aromatics), 8.89 (1H, br s, -N<u>H</u>-N=); MS: 324 *m/z* (M^+). *Anal.* Calcd for $C_{14}H_{13}ClN_2O_3S$: C, 51.77; H, 4.03; N,8.63. Found: C, 51.81; H, 4.06; N, 8.70.

1-(2-Thenyl)oxyethyl-2-[2-(1-chloro-2-methoxy-2-oxoethylidene)hydrazino]benzene (**3b**) (0.91 g, 67%) as white needles having mp 71°C; IR (Nujol): 3310, 1720 (cm^{-1}); ^{1}H-NMR: 3.31 (2H, t, *J* = 6.3, -C<u>H</u>$_2$CH$_2$-), 3.89 (3H, s, C<u>H</u>$_3$OOC-), 4.30 (2H, t, *J* = 6.3, -C<u>H</u>$_2$CH$_2$-), 6.8-7.6 (7H, m, aromatics), 8.80 (1H, br s, -N<u>H</u>-N=); MS: 338 *m/z* (M^+). *Anal.* Calcd for $C_{15}H_{15}ClN_2O_3S$: C, 53.18; H, 4.46; N, 8.27. Found: C, 53.21; H, 4.49; N, 8.33.

1-(3-Thenyl)oxymethyl-2-[2-(1-chloro-2-methoxy-2-oxoethylidene)hydrazino]benzene (**3c**) (0.97 g, 75%) as pale yellow needles having mp 69°C; IR (Nujol): 3320, 1730 (cm^{-1}); ^{1}H-NMR: 3.90 (3H, s, C<u>H</u>$_3$OOC-), 5.20 (2H, s, -C<u>H</u>$_2$O-), 6.9-7.6 (7H, m, aromatics), 8.80 (1H, br s, -N<u>H</u>-N=); MS: 324 *m/z* (M^+). *Anal.* Calcd for $C_{14}H_{13}ClN_2O_3S$: C, 51.77; H, 4.03; N,8.63. Found: C, 51.80; H, 4.09; N, 8.71.

1-(2-Furyl)methyl 2-[2-(1-chloro-2-methoxy-2-oxoethylidene)hydrazino]benzoate (**8a**) (1.01 g, 75%) as pale yellow prisms having mp 69°C; IR (Nujol): 3330, 1730, 1720 (cm^{-1}); ^{1}H-NMR: 3.90 (3H, s, C<u>H</u>$_3$OOC-), 5.31 (2H, s, -C<u>H</u>$_2$O-), 6.8-7.4 (7H, m, aromatics), 8.75 (1H, br s, -N<u>H</u>-N=); MS: 336 *m/z* (M^+). *Anal.* Calcd for $C_{15}H_{13}ClN_2O_5$: C, 53.50; H, 3.89; N, 8.32. Found: C, 53.55; H, 3.85; N, 8.39.

1-(3-Furyl)methyl 2-[2-(1-chloro-2-methoxy-2-oxoethylidene)hydrazino]benzoate (**8b**) (0.90 g, 67%) as colourless prisms having mp 83°C; IR (Nujol): 3320, 1740, 1720 (cm^{-1}); ^{1}H-NMR: 3.89 (3H, s, C<u>H</u>$_3$OOC-), 5.27 (2H, s, -C<u>H</u>$_2$O-), 6.8-7.4 (7H, m, aromatics), 8.90 (1H, br s, -N<u>H</u>-N=); MS: 336 *m/z* (M^+). *Anal.* Calcd for $C_{15}H_{13}ClN_2O_5$: C, 53.50; H, 8.32; N,8.32. Found: C, 53.48; H, 3.84; N, 8.37.

Reaction of hydrazonoyl chlories (3) and (8) in the presence of silver carbonate. A solution of (**3**) or (**8**) (1.0 mmol) in dry dioxane (50 mL) was treated with Ag_2CO_3 (1.10 g, 4.0 mmol) at rt in the dark for 120 h. The undissolved material was filtered off and the solvent was evaporated under reduced pressure.

In the case of hydrazonoyl chlorides (**3a**) and (**3b**) the residue was chromatographed on a silica gel column with Et_2O-hexane 5:1 affording (**5a**) and (**5b**), respectively.

1-[(2-Thenyl)-2-oxymethyl]phenyl-3,5-bis methoxycarbonyl-1,2,4-triazole (**5a**) (78 mg, 21%) as yellow needles having mp 108°C (from diisopropyl ether); IR (Nujol): 1740, 1730 (cm^{-1}); ^{1}H-NMR: 3.94 (6H, s, C$\underline{H}_3$OOC-), 5.28 (2H, s, -C$\underline{H}_2$O-), 6.9-7.5 (7H, m, aromatics); MS: 373 *m/z* (M^+). *Anal.* Calcd for $C_{17}H_{15}N_3O_5S$: C, 54.68; H, 4.05; N, 11.25. Found: C, 54.71; H, 4.02; N, 11.31.

1-[(2-Thenyl)-2-oxyethyl]phenyl-3,5-bis methoxycarbonyl-1,2,4-triazole (**5b**) (81 mg, 21%) as pale yellow needles having mp 79°C (from diisopropyl ether); IR (Nujol): 1730, 1720 (cm^{-1}); ^{1}H-NMR: 3.23 (2H, t, *J* = 7.2, -C$\underline{H}_2$CH$_2$-), 3.99 (6H, s, C$\underline{H}_3$OOC-), 4.22 (2H, t, *J* = 7.2, -C$\underline{H}_2$CH$_2$-), 6.79 (1H, dd, *J* = 3.4, 1.1, thenyl-$\underline{H}_3$), 6.87 (1H, dd, *J* = 5.2, 3.4, thenyl-$\underline{H}_4$), 7.02-7.07 (2H, m, aromatics), 7.09 (1H, dd, *J* = 5.2, 1.1, thenyl-$\underline{H}_5$), 7.42-7.53 (2H, m, aromatics); MS: 387 *m/z* (M^+). *Anal.* Calcd for $C_{18}H_{17}N_3O_5S$: C, 55.81; H, 4.42; N, 10.85. Found: C, 55.78; H, 4.38; N, 10.90.

In the case of hydrazonoyl chloride (**3c**) the residue was chromatographed on a silica gel column with CH_2Cl_2-EtOAc 20:1 affording tricyclic product (**6**).

Thieno[3,2-*d*][1,4]benzoxazino[1,5-*b*]pyrazole (**6**) (0.11 g, 37%) as white powder having mp 67°C (from diisopropyl ether); IR (Nujol): 1730 (cm^{-1}); ^{1}H-NMR: 3.92 (3H, s, C$\underline{H}_3$OOC-), 4.10 (1H, d, *J* = 11.8, -C$\underline{H}_2$-), 4.66 (1H, d, *J* = 11.8, -C$\underline{H}_2$-), 4.80 (1H, s, C-$\underline{H}$), 5.44 (1H, d, *J* = 3.4, thenyl-$\underline{H}_4$), 5.90 (1H, d, *J* = 3.4, thenyl-$\underline{H}_5$), 6.9-7.3 (4H, m, aromatics); ^{13}C-NMR: 51.16 (q, $\underline{C}H_3$O-), 54.40 (d, C_{2a}), 69.28 (t, C_6), 76.78 (s, C_{5a}), 98.16 (d, C_5), 107.80 (d, C_4), 116.0-121.0, 141.63 (s, C_2), 176.89 (s, -$\underline{C}$OO-); MS: 288 *m/z* (M^+). *Anal.* Calcd for $C_{14}H_{12}N_2O_3S$: C, 58.32; H, 4.19; N, 9.72. Found: C, 58.28; H, 4.22; N, 9.79.

In the case of hydrazonoyl chloride (**8a**) the residue was chromatographed on a silica gel column with diethylether. First fractions contained 1,2,4-triazole (**10**), further elution gave oxalamide (**11**).

1-[(2-Furyl)-2-carboxymethyl]phenyl-3,5-bis methoxycarbonyl-1,2,4-triazole (**10**) (39 mg, 10%) as white needles having mp 88°C (from diisopropyl ether); IR (Nujol): 1740, 1730 (cm^{-1}); ^{1}H-NMR: 4.04 (6H, s, C$\underline{H}_3$OOC-), 5.37 (2H, s, -C$\underline{H}_2$O-), 6.4-7.4 (7H, m, aromatics); MS: 385 *m/z* (M^+). *Anal.* Calcd for $C_{18}H_{15}N_3O_7$: C, 56.11; H, 3.92; N, 10.90. Found: C, 56.15; H, 3.95; N, 10.96.

N-[(2-Furyl)-2-carboxymethyl]phenyl oxalamide monomethylester (**11**) (27 mg, 9%) as white powder having mp 136°C (from diisopropyl ether); IR (Nujol): 1740, 1730, 1650 (cm^{-1}); ^{1}H-NMR: 4.00 (3H, s, C$\underline{H}_3$OOC-), 5.36 (2H, s, -C$\underline{H}_2$O-), 6.4-8.0 (7H, m, aromatics), 12.50 (1H, br s, -N$\underline{H}$-); MS: 303 *m/z* (M^+). *Anal.* Calcd for $C_{15}H_{13}NO_6$: C, 59.41; H, 4.32; N, 4.62. Found: C, 59.37; H, 4.35; N, 4.70.

In the case of hydrazonoyl chloride (**8b**) the residue was chromatographed on a silica gel column with dichloromethane affording tricyclic product (**12**).

Furo[3,2-*d*][1,4]benzoxazepino[1,5-*b*]pyrazole (**12**) (93 mg, 31%) as white powder having mp 94°C (from diisopropyl ether); IR (Nujol): 1740, 1725 (cm^{-1}); ^{1}H-NMR: 3.99 (3H, s, C$\underline{H}_3$OOC-), 4.34 (1H, d, *J* = 12.6, -C$\underline{H}_2$-), 4.52 (1H, d, *J* = 12.6, -C$\underline{H}_2$-), 5.37 (1H, s, C-$\underline{H}$), 5.66 (1H, d, *J* = 4.2, furyl-$\underline{H}_4$), 6.39 (1H, d, *J* = 4.2, furyl-$\underline{H}_5$), 6.9-7.6 (4H, m, aromatics); ^{13}C-NMR: 50.12 (q, $\underline{C}H_3$O-), 63.30 (t, C_6), 76.80 (d, C_{5a}), 84.33 (s, C_{2a}), 107.80 (d, C_5), 112.0-120.0, 138.65 (d, C_4), 140.20 (s, C_2), 168.45 (s, -$\underline{C}$OO-), 173.90 (s,

C_8); MS: 300 *m/z* (M^+). *Anal.* Calcd for $C_{15}H_{12}N_2O_5$: C, 60.00; H, 4.03; N, 9.33. Found: C, 59.96; H, 3.99; N, 9.40.

Computational Details

The geometry of (**6**), of the corresponding transition state (**TS6**), and of the nitrilimine (**4c**) were fully optimized at the B3LYP/cc-pVDZ level. The nature of the energy minimum structures of nitrilimine intermediate, tetracyclic product (**6**) and of the transition state (**TS6**) were confirmed by harmonic analysis. All computations were carried out by the Gaussian 03 suite.[11]

ACKNOWLEDGEMENTS

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