Questa è la versione referata di quella pubblicata il 28 Agosto 2017:

https://pubs.acs.org/doi/10.1021/acs.joc.7b02135

Divergent Approach to Thiazolylidene derivatives: a new Perspective in the Synthesis of Heterocyclic Skeleton from β-Amidothioamides Reactivity

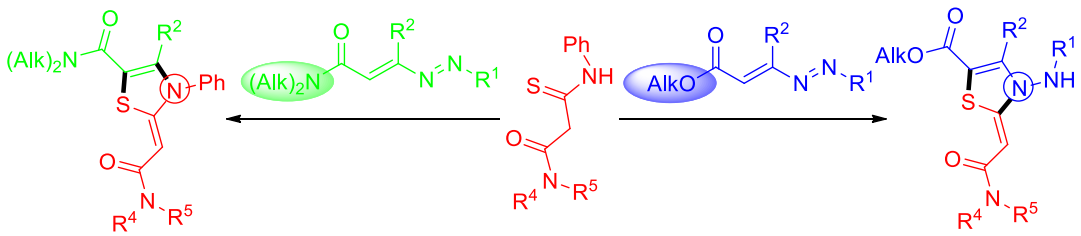
Stefania Santeusanio,[†] Roberta Majer,[†] Francesca Romana Perrulli,[†] Lucia De Crescentini,[†] Gianfranco Favi,[†] Gianluca Giorgi,[‡] and Fabio Mantellini[†]*

†Department of Biomolecular Sciences, Section of Organic Chemistry and Organic Natural Compounds, University of Urbino "Carlo Bo", Via I Maggetti 24, 61029 Urbino, Italy

‡Department of Chemistry, University of Siena, Via Aldo Moro, 53100 Siena, Italy

*E-mail: stafania.santeusanio@uniurb.it

Table of contents



Abstract

Herein we report a domino protocol able to reach regioselectively thiazolylidene systems by combining the reactive peculiarities both of β-amidothioamides (ATAs) and 1,2-diaza-1,3-dienes (DDs). Depending on the reaction conditions and/or the nature of the residue at C4 of the heterodiene system, ATAs can act as hetero mononucleophiles or hetero dinucleophiles in the diversified thiazolylidene ring assembly.

Introduction

Design and development of domino reactions[1] that provide structural/skeletal diversity with economies of step for the creation of functional-oriented compounds are an important and challenging area in modern synthetic organic chemistry. The value of a domino reaction can be correlated to the number of bonds generated in such a process in one single event. In this context, the synthesis of structures containing privileged thiazoline framework becomes important because of their biological and pharmacological properties.[2] In particular, some thiazolylidenes with general structure (I) and (II) have been reported as the basis for cannabinoid receptor ligands (Figure 1).[3]

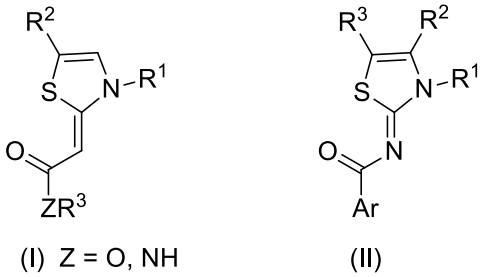


Figure 1. Examples of biologically active thiazolylidenes.

In recent years, β-ketothioamides[4] (KTAs) have emerged as powerful synthons with different dinucleophilic centres (S and N; C and N; C and S atoms) (Figure 2) that may react with dielectrophilic reagents allowing the construction of important heterocyclic scaffolds[4-6] but their use as functional tools for variously functionalized thiazolylidene structure of type (I) (Figure 1) is scarcely represented thus far.[5,7]

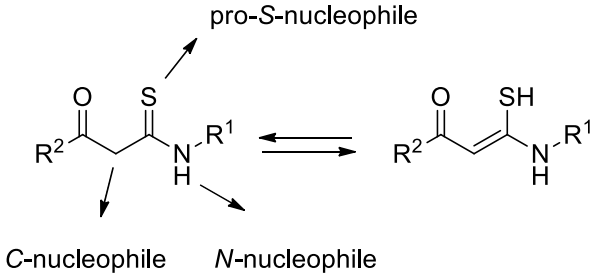


Figure 2. Nucleophilic profile of KTAs.

Only accidentally, functionalized thiazolylidenes have been synthesized from KTAs and malononitrile by the group of Bogdanowicz-Szwed during their studies for the preparation of pyridine compounds.[5] Recently, Ming Li and co-authors reported a regioselective synthesis of thiazolylidenes by I_2-controlled self-condensation reaction of KTAs.[7]

1,2-Diaza-1,3-dienes (DDs)[8] are well-known as performing Michael acceptors owing to the presence of the azo electron-withdrawing group in the conjugated system. By exploiting our experience in the field of *S*-nucleophilic addition to DD as first event that can evolve in an intramolecular ring closure producing *S*,*N*-containing heterocyclic derivatives,[9] we have recognized the β-amidothioamides (ATAs), slightly modified KTAs, as potential nucleophilic candidates for obtaining new and interesting thiazolylidene derivatives (Figure 3).

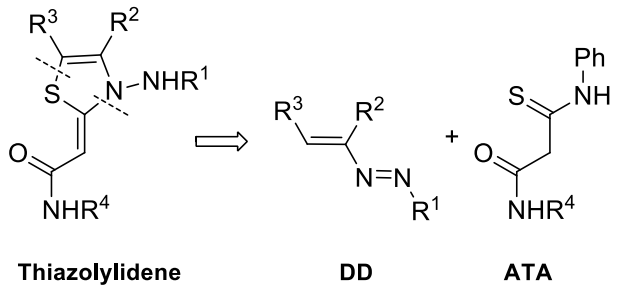
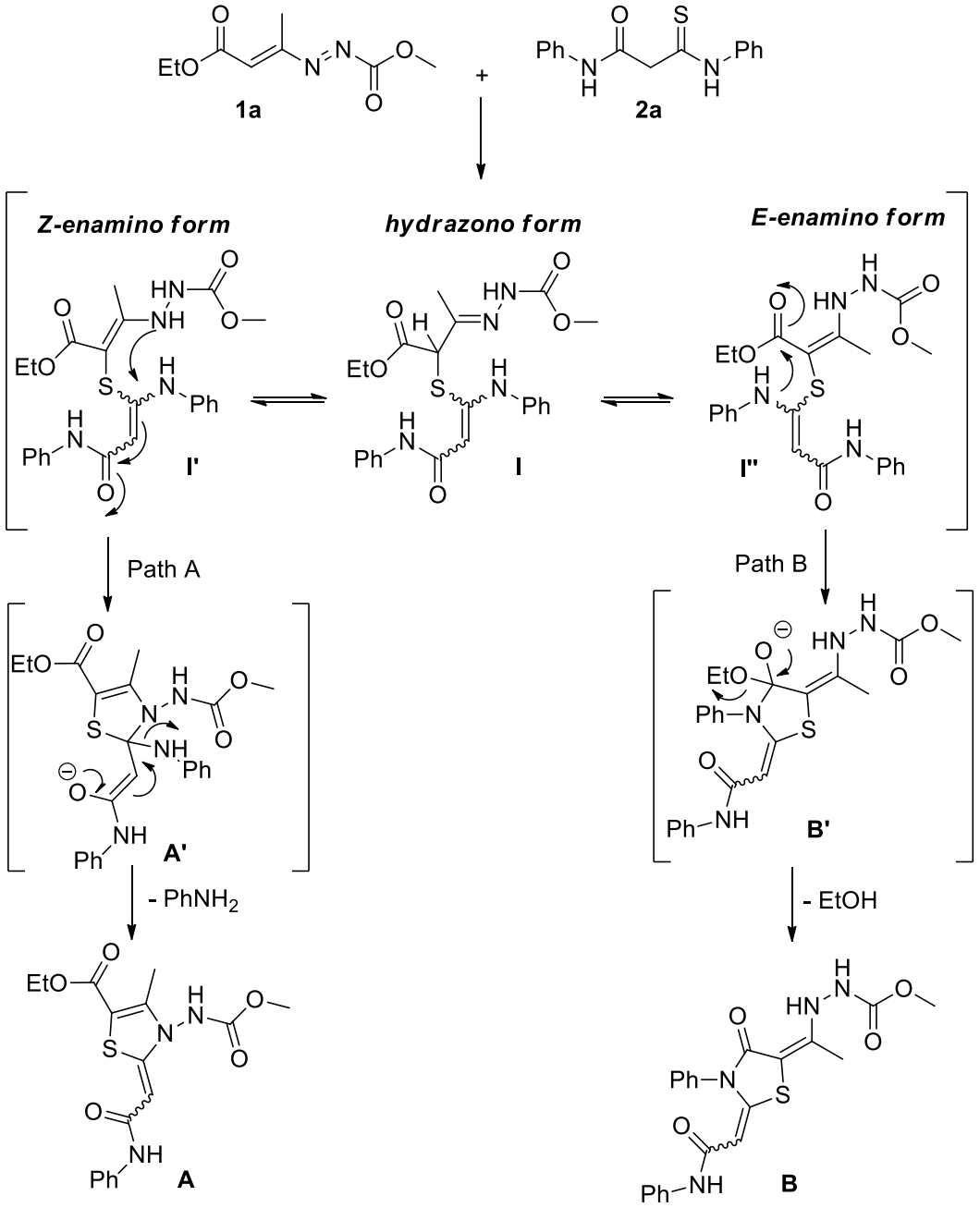


Figure 3. Our hypothesized disconnection of thiazolylidene type (I) derivatives.

We initially investigated the reaction between DD **1a** and ATA **2a**, choosen as representative model, in methanol at room temperature (Table 1, entry 1). Two products were isolated and identified as thiazolylidene derivatives **A** and thiazolidin-4-one compounds **B**. Based on our experience,[9a,e] we have evaluated that the reaction might proceed in different ways, as shown in Scheme 1. The *S*-nucleophilic attack at C4 of the azo-ene system affords the initial thia-Michael adduct **I**. A subsequent internal *N*-nucleophilic attack could produce divergent intramolecular cyclizations to form the thiazolylidene ring **A** (Path A, Scheme 1), or to provide the thiazolidin-4-one ring system **B** (Path B, Scheme 1). The thia-Michael adduct exhibits a tautomeric equilibrium between the hydrazono form **I** and the enamino form both in *Z* (**I'**) and *E* (**I"**) configurations, and different reaction conditions can affect on this equilibrium.

Scheme 1 Illustrative ring closure pathways of the initial *S*-Michael adduct.



It is noteworthy that the regioselectivity in the ring closure process is guided by the equilibrium between the possible tautomeric forms of the initial thia-Michael adduct.

In fact, probably when thia-Michael adduct is in *Z*-enamino configuration (**I'**), the proximity of the nitrogen to the conjugated system deriving from the starting ATA **2a** favors the formation of the desired thiazolylidene **A** (Path A, Scheme 1). This cyclization is disadvantaged when the thia-

Michael adduct is in hydrazono (**I**) or *E*-enamino (**I'**) forms. In those cases, the ring closure process proceeds through a nucleophilic attack of the nitrogen derived from the ATA to the ester function leading to the thiazolidin-4-one derivative **B** (Path B, Scheme 1).

In an attempt to control the regiochemistry of the process, we have enlarged our studies testing a range of different solvents and adding to the reaction medium some organic bases in different ratios (Table 1).

Table 1. Optimization of the reaction conditions between DD **1a** and ATA **2a**.[a]

Run	Base (equiv.)	Solvent (5 mL)	Time (h)	Yield **A** (%)[d]	Yield **B** (%)[d]
1	none	MeOH	1.5[b] (16)[c]	39	7
2	none	THF	1.5[b] (16)[c]	36	5
3	none	DMF	1.5[b] (16)[c]	37	5
4	**none**	**$CHCl_3$**	**1**[b] (16)[c]	**87**	**n.d.**
5	DIPEA (1)	$CHCl_3$	0.2[b] (16)[c]	35	51
6	DIPEA (0.5)	$CHCl_3$	0.5[b] (16)[c]	30	19
7	DMAP (0.5)	$CHCl_3$	0.5[b] (16)[c]	traces	38
8	DABCO (0.5)	$CHCl_3$	0.5[b] (16)[c]	10	34
9	DIPEA (0.5)	MeOH	0.5[b] (16)[c]	15	27

[a] Reaction conditions: **1a** (1.0 mmol, 1 equiv.) and **2a** (1.0 mmol, 1 equiv.) were solved in 5 mL of solvent and stirred at room temperature; [b] Referred to the disappearance of the reagents; [c] Referred to the complete conversion of the intermediate **I**; [d] Yield of pure isolated compound.

By the evidence of data summarized in Table 1 (entries 1-3), the use of solvents such as MeOH, THF or DMF without base leads to poor results both in the regioselectivity of the annulation and in yields. The presence of an organic base in $CHCl_3$ or MeOH generally favors the formation of the thiazolidin-4-one derivative **B** over the thiazolylidene derivative **A**. This fact resulted in accordance

to that observed by Singh and co-workers for base-catalyzed reactions of KTAs and conjugated systems like alkynoates.[6a] To direct the regioselectivity toward the desired thiazolylidene **A**, the best reaction conditions found require the employ of $CHCl_3$ at room temperature (Table 1, entry 4).

Under these optimized conditions, we then explored the generality of this protocol employing different 4-alkoxycarbonyl or 4-aminocarbonyl DDs **1a-e** (1.0 eq.) and variously substituted ATAs **2a-c** (1.0 eq.) synthesized by literature method.[10]

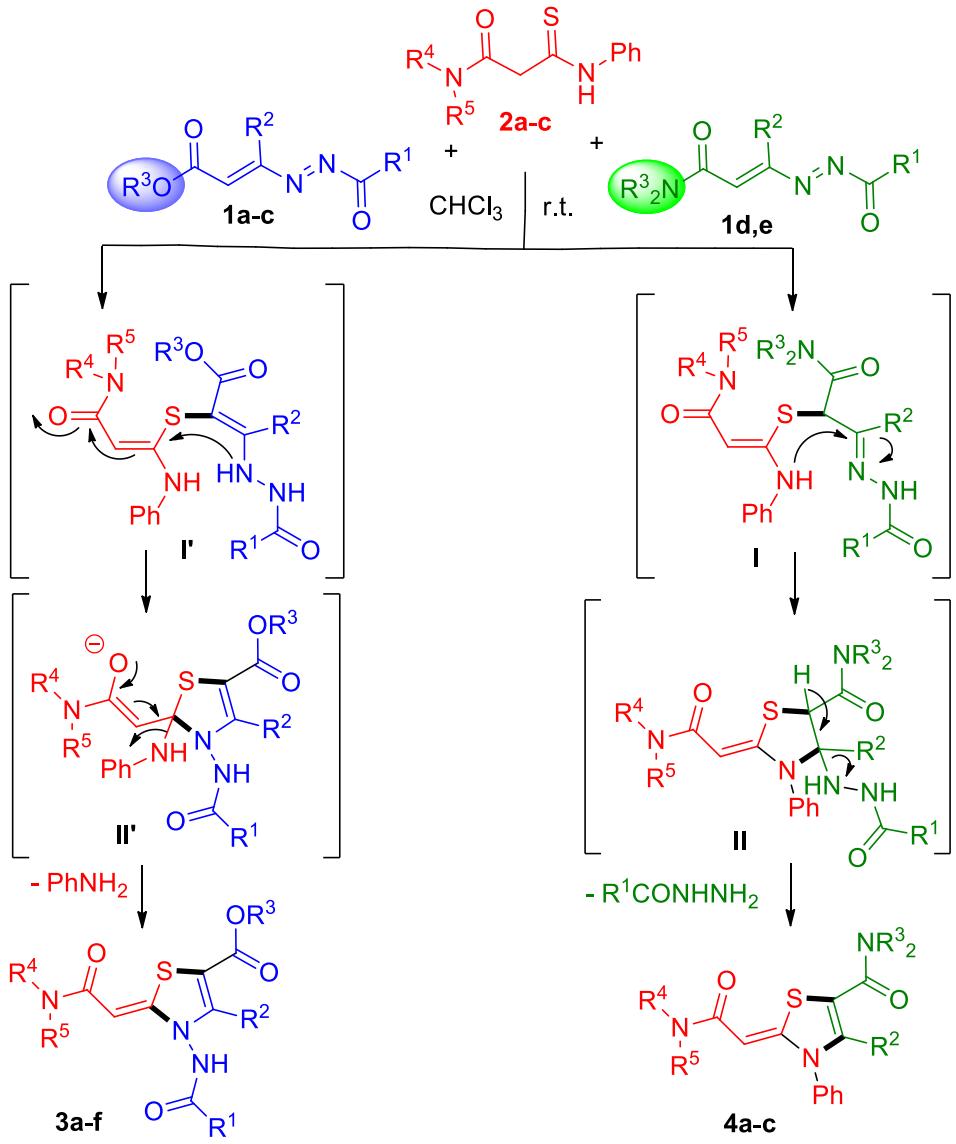
After the quick disappearance of the starting materials (0.2-1.5 h: the progress was monitored looking at the change of the reaction mixtures from the initial red colour of DD **1** to the final pale yellow one and by tlc), the reactions were left at room temperature overnight for the complete conversion of the initial spot attributable to the intermediate **I**.[11]

It should be emphasized that when DDs **1a-c** bearing an ester function at C4 of the azo-ene system are employed, ATAs **2a-c** do not behave as dinucleophiles in the heterocycle assembly.

Indeed, after the initial thia Michael addition of the sulphur of ATAs **2** to the terminal carbon atom of the azo-ene system of DDs **1** (Scheme 2; Table 2), the intramolecular ring closure (intermediate **I'**) takes place by a regioselective nucleophilic vinylogous attack of the enamine nitrogen at the conjugated system deriving from the starting ATAs. The final conjugated elimination of the aniline molecule from **II'** affords the thiazolylidene derivatives **3a-f** (Scheme 2). Summing up, in this cyclization, the ATAs **2a-c** behave initially as sulphur nucleophile and subsequently as electrophile, acting as Michael acceptor. On the contrary, replacing in DD **1d-e** the ester function at C4 with the amide one (Scheme 2, Table 2), ATAs **2a-c** operate, as usually observed, namely as hetero-dinucleophile synthons. In these latter cases, the ring closure of the initial thia-Michael adduct **I** is carried out by the nucleophilic attack of the aniline nitrogen to the electrophilic hydrazone function with formation of thiazolidin-2-ylidene intermediate **II**. The loss of the hydrazine moiety produces the final thiazolylidenes **4a-c**. This different course is probably attributable to the lower acidity of

the protons in α-position to the amide function of the adduct intermediates that favors the hydrazone form **I** of the thia-Michael adduct.

Scheme 2. Different ring closure pathways in the reaction between ATAs **2a-c** and 4-alkoxycarbonyl DDs **1a-c** or 4-aminocarbonyl DDs **1d,e**.[a]

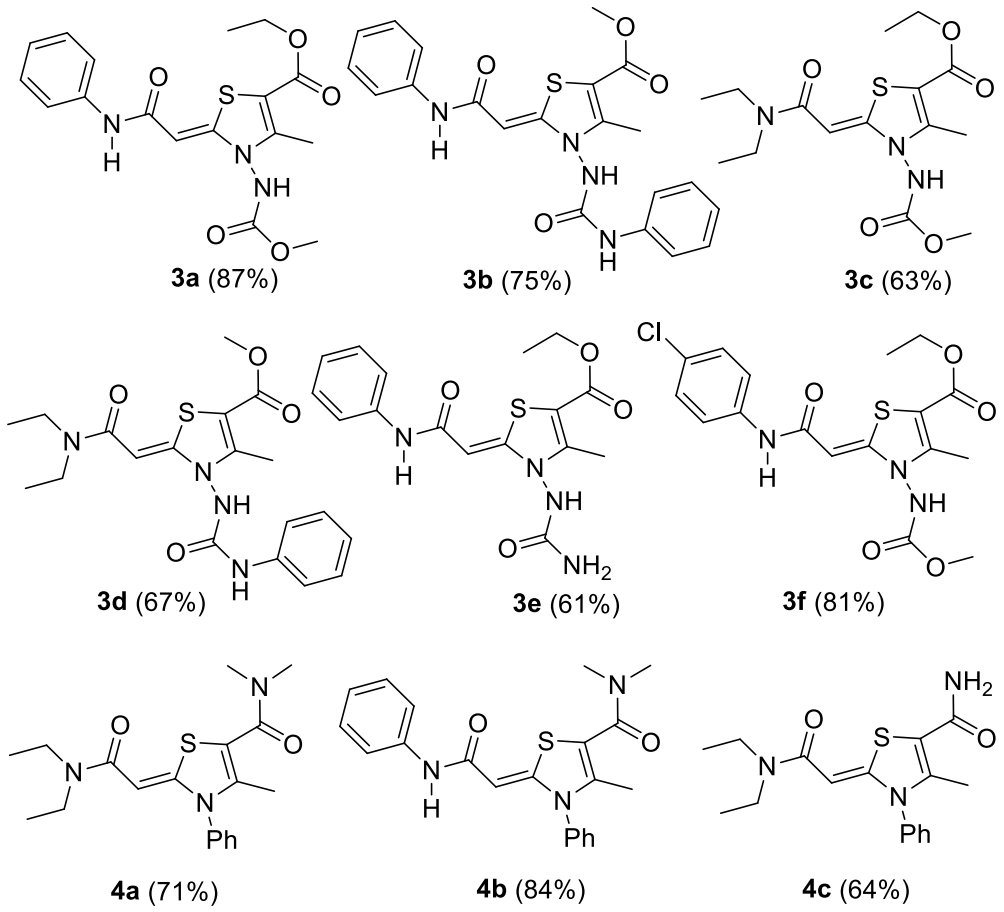


[a] Reaction conditions: **1** (1.0 mmol, 1 equiv), **2** (1.0 mmol, 1 equiv), $CHCl_3$ (5mL), r.t.

Some differences in the assembly of the thiazolylidene skeleton can be observed: in the synthesis of compounds **3a-f** (Scheme 2), the heterocyclic nitrogen comes from the azo-ene system of DD **1** which participates in the construction of the ring also with two carbon atoms. Differently, in the preparation of thiazolylidenes **4a-c**, the nitrogen derives from the ATAs **2** and DDs **1** contributes to

the ring assembly only with two carbon atoms. This occurrence permits an additional diversification site in the obtained thiazolylidenes.

Table 2. Substrate scope in the reaction between ATAs **2a-c** and 4-alkoxycarbonyl DDs **1a-c** or 4-aminocarbonyl DDs **1d,e**.[a]



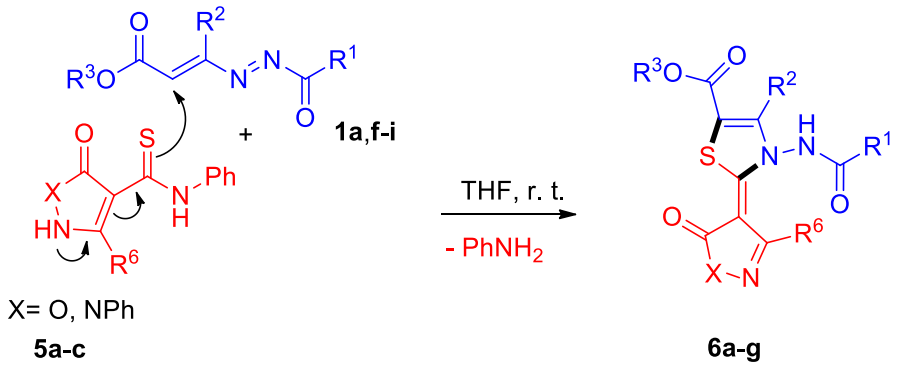
[a] Yield of pure isolated product.

The *Z*-configuration of exocyclic double bond at C2 of the thiazolylidene derivatives **3a-f**, **4a-c** was determined by NOESY experiments on the representative compounds **3c** and **4c**.

To assess the applicability of this synthetic strategy, attempts to expand the substrate scope and amplify molecular diversity showed to be successful also in the case of heterocyclic ATAs **5a-c**[12] and 4-alkoxycarbonyl DDs **1a**,**f-i**. The reactions were conducted in THF at room temperature, affording new thiazolylidene-based bicyclic systems **6a-g** in good yields (62-85%) (Scheme 3;

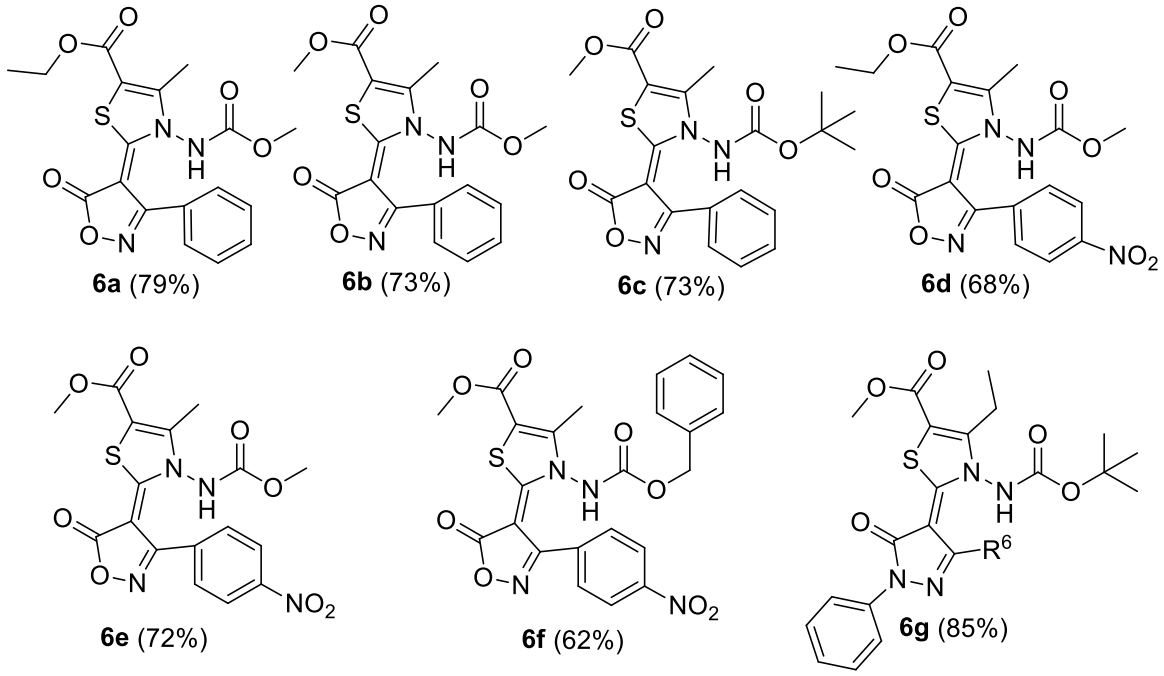
Table 3). Unfortunately, the reactions between 4-aminocarbonyl DDs **1d,e** and heterocyclic ATAs **5a-c** furnished complicate reaction mixtures.

Scheme 3. Synthesis of double bond-linked bi-heterocycles **6a-g**.[a]



[a] Reaction conditions: **1** (1.0 mmol, 1 equiv), **5** (1.0 mmol, 1 equiv), THF (5mL), r.t.

Table 3. Substrate scope in the reaction between heterocyclic ATAs **5a-c** and DDs **1a**,**f-i**.[a]



[a] Yield of pure isolated product.

The structures of all new synthesized double bond-linked bi-heterocycles **6a-g** were determined by their spectral (^{1}H, ^{13}C NMR, MS) studies and unequivocally confirmed by the X-ray single crystal diffraction analysis on **6d** as representative compound of the series (Figure 4).

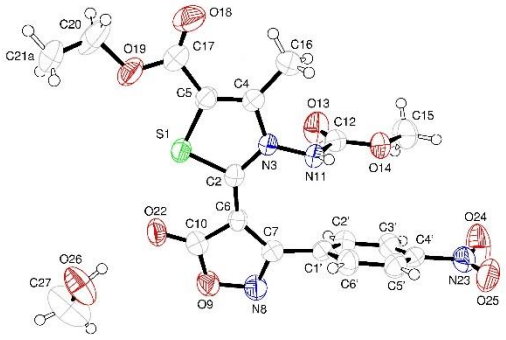


Figure 4. Crystal structure of **6d**. Ellipsoids enclose 50% probability.[13]

In conclusion, we have developed with success a regioselective one-pot synthesis of new thiazolylidene derivatives by reaction of DDs and ATAs in a proper solvent without base catalyst or activator. Importantly, this domino protocol provides flexible substitution patterns both in DDs and in ATAs. Depending on the nature of the substituent at C4 of DD, ATA contributes to the construction of the thiazolylidene ring with two (S-C) or three (S-C-N) atoms by means of formal [3+2] or [2+3] annulations. Moreover, this protocol is resulted successfully applicable to heterocyclic ATAs affording double bond-linked bi-heterocyclic scaffolds. Further investigations to expand the scope of this method are currently underway by our research group.

Experimental Section

General Remarks

All chemicals and solvents were purchased from commercial suppliers and used as received. 1,2-Diaza-1,3-dienes were prepared as reported[8a,14] and used as *EE*/*EZ* isomer mixtures. β-Amidothioamides derivatives were prepared following the literature methods.[10,12] FT-IR spectra were obtained as Nujol mulls. Melting points were measured with a Gallenkamp apparatus. NOESY, 2D experiments, ^{1}H and ^{13}C spectra were recorded on Varian Mercury 400 MHz or on Bruker Avance. ^{1}H (400 MHz) and ^{13}C (100 MHz) spectra were recorded in DMSO-d_6 or in $CDCl_3$.

Chemical shifts (δ_H) are reported in parts per million (ppm), relative to TMS as internal standard, whereas (δ_C) are referred to the middle peak of DMSO-d_6 or of $CDCl_3$.as internal standards.

All coupling constant (J values) are given in hertz (Hz). The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; ArH, aromatic hydrogen. All the NH and NH2 exchanged with D2O. Precoated silica gel plates 0.25 mm were employed for analytical thin layer chromatography and silica gel 35-70 μm for column chromatography. Mass spectra were obtained by EI (70eV) or by ESI-MS analyses. Elemental analyses were within ± 0.4 of the theoretical values (C, H, N).

Experimental procedures and spectral data.

General procedure for the synthesis of thiazolylidene derivatives 3a-f and 4a-c: To a magnetically stirred solution of ATAs **2a-c** (1.0 mmol) in $CHCl_3$ (5 mL) the appropriate DDs **1a-e** (1.0 mmol) was added at room temperature. After the disappearance of the reagents (0.2-1.5 h) (TLC check), the reaction was left at room temperature overnight for the complete conversion of the intermediate to the final product (15-18 h). Then, the solvent was removed *in vacuo*; in some cases, solid derivatives **3** or **4** were obtained by crystallization from appropriate solvent or solvent mixtures. In other cases, a chromatographic purification (cyclohexane/ethyl acetate mixtures) followed by crystallization from appropriate solvents was necessary.

Methyl 2-{2-[4-oxo-2-(2-oxo-2-anilinoethylidene)-3-phenylthiazolidin-5-ylidene]ethyl}hydrazinecarboxylate B. Light yellow powder, (from EtOAc-light petroleum ether). IR (Nujol, cm^{-1}) ν_{max} 3320, 3257, 1704, 1664, 1635, 1596, 1536. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.02 and 2.32 (2s, 3H, CH_3), 3.64 and 3.68 (2s, 3H, OCH_3), 5.08 and 5.21 (2s, 1H, CH), 6.90-6.95 (m, 1H, ArH), 7.18-7.39 (m, 4H, ArH), 7.49-7.63 (m, 5H, ArH), 8.31 and 8.86 (2s, 1H, NH), 9.54, 9.63 and 9.74 (3s, 2H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 16.22, 52.3, 52.4, 79.1, 89.0, 90.0, 118.1, 118.2, 121.9, 122.1, 128.5, 128.6, 128.7, 129.1, 129.7, 129.9, 135.6, 136.5, 139.9, 140.1,

152.5, 165.0, 165.3, 166.0. ESI-MS 425.1 $[M+H]^+$. Anal.: calcd. for $C_{21}H_{20}N_4O_4S$ (424.12): C, 59.42; H, 4.75; N, 13.20. Found: C, 59.59; H, 4.65; N, 13.12.

Ethyl 2-[2-anilino-2-oxoethylidene]-3-[(methoxycarbonyl)amino]-4-methyl-2,3-dihydro-1,3-thiazole-5-carboxylate (3a). Yield: 328.3 mg (87%). Beige powder, mp: 220-222 °C (from EtOH). IR (Nujol, cm^{-1}) ν_{max} 3382, 3149, 1744, 1705, 1636, 1598, 1552. ^1H NMR (400 MHz, DMSO-d_6) δ: 1.28 (t, J = 8.0 Hz, 3H, OCH_2CH_3), 2.34 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 4.25 (q, J = 8.0 Hz, 2H, OCH_2CH_3), 5.62 (s, 1H, CH), 6.94 (t, J = 8.0 Hz, 1H, ArH), 7.24 (t, J = 8.0 Hz, 2H, ArH), 7.59 (d, J = 8.0 Hz, 2H, ArH), 9.56 (s, 1H, NH), 10.70 (br s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 11.4, 14.1, 53.1, 60.6, 84.0, 102.0, 118.0, 121.8, 128.5, 140.2, 147.0, 154.9, 155.3, 161.5, 165.2. MS (EI): m/z (%) 377 [M^+, (22)], 332 (4), 299 (16), 285 (100). Anal.: calcd. for $C_{17}H_{19}N_3O_5S$ (377.41): C, 54.10; H, 5.07; N, 11.13. Found: C, 54.26; H, 5.18; N, 11.06.

Methyl 3-[(anilinocarbonyl)amino]-2-[2-anilino-2-oxoethylidene]-4-methyl-2,3-dihydro-1,3-thiazole-5-carboxylate (3b). Yield: 318.3 mg (75%). Whitish solid, mp: 181-184 °C (from MeOH). IR (Nujol, cm^{-1}) ν_{max} 3332, 1720, 1705, 1685, 1629, 1600, 1560. ^1H NMR (400 MHz, DMSO-d_6) δ: 2.36 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 5.65 (s, 1H, CH), 6.92 (t, J = 8.0 Hz, 1H, ArH), 7.02 (t, J = 8.0 Hz, 1H, ArH), 7.23 (t, J = 8.0 Hz, 2H, ArH), 7.30 (t, J = 8.0 Hz, 2H, ArH), 7.50 (d, J = 8.0 Hz, 2H, ArH), 7.57 (d, J = 8.0 Hz, 2H, ArH), 9.40 (s, 1H, NH), 9.68 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 11.8, 51.8, 84.2, 101.5, 118.1, 118.2, 118.8, 121.9, 122.8, 128.7, 128.8, 138.9, 140.4, 148.5, 152.8, 156.3, 162.3, 165.5. MS (EI): m/z (%) 424 [M^+, (6)], 331 (29), 274 (88), 239 (100), 213 (63), 119 (72). Anal.: calcd. for $C_{21}H_{20}N_4O_4S$ (424.47): C, 59.42; H, 4.75; N,13.20 Found: C, 59.51; H, 4.85; N,13.11.

Ethyl 2-[2-(diethylamino)-2-oxoethylidene]-3-[(methoxycarbonyl)amino]-4-methyl-2,3-dihydro-1,3-thiazole-5-carboxylate (3c). Yield: 225.18 mg (63%). Beige powder, mp: 188-190 °C (from MeOH). IR (Nujol, cm^{-1}) ν_{max} 3153, 2980, 1755, 1685, 1621, 1599, 1522. ^1H NMR (400 MHz, DMSO-d_6) δ: = 1.06 (br s, 6H, 2 x NCH_2CH_3), 1.27 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 2.31 (s,

3H, CH_3), 3.26 (br s, 4H, 2 x NC*H*$_2$CH$_3$), 3.75 (s, 3H, OCH_3), 4.22 (q, *J* = 7.2 Hz, 2H, OC*H*$_2$CH$_3$), 5.49 (s, 1H, CH), 10.70 (br s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 11.5, 14.1, 41.1, 53.1, 60.4, 80.2, 101.8, 147.0, 155.2, 156.3, 161.7, 165.6. MS (EI): m/z (%) 357 [M^+, (78)], 325 (10), 312 (16), 285 (91), 258 (100), 100 (23). Anal.: calcd. for $C_{15}H_{23}N_3O_5S$ (357.43): C, 50.41; H, 6.49; N, 11.76. Found: C, 50.25; H, 6.35; N, 11.79.

Methyl 3-[(anilinocarbonyl)amino]-2-[2-(diethylamino)-2-oxoethylidene]-4-methyl-2,3-dihydro-1,3-thiazole-5-carboxylate (3d). Yield: 271.0 mg (67%) Whithish powder, mp: 190-192 °C (from EtOH). IR (Nujol, cm^{-1}) ν_{max} 3298, 3207, 3140, 1726, 1690, 1624, 1585, 1560. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.02 (t, *J* = 6.8 Hz, 6H, 2 x NCH$_2$C*H*$_3$), 2.35 (s, 3H, CH_3), 3.21-3.28 (m, 4H, 2 x NC*H*$_2$CH$_3$), 3.75 (s, 3H, OCH_3), 5.58 (s, 1H, CH), 7.01 (t, *J* = 7.6 Hz, 1H, ArH), 7.28 (t, *J* = 7.6 Hz, 2H, ArH), 7.44 (d, *J* = 7.6 Hz, 2H, ArH), 9.35 (s, 1H, NH), 9.50 (br s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 11.9, 13.9, 41.1, 51.7, 80.3, 101.1, 119.0, 122.7, 128.7, 138.8, 148.5, 153.1, 157.0, 162.3, 165.7. MS (EI): m/z (%) 404 [M^+, (28)], 311 (27), 305 (23), 213 (68), 186 (63), 119 (51), 100 (100). Anal.: calcd. for $C_{19}H_{24}N_4O_4S$ (404.48): C, 56.42; H, 5.98; N, 13.85. Found: C, 56.28; H, 6.09; N, 13.92.

Ethyl 3-[(aminocarbonyl)amino]-2-[2-anilino-2-oxoethylidene]-4-methyl-2,3-dihydro-1,3-thiazole-5-carboxylate (3e). Yield: 221.0 mg (61%). Beige powder, mp 216-218 °C from EtOH). IR (Nujol, cm^{-1}) ν_{max} 3390, 3315, 3276, 3215, 3125, 1699, 1684, 1674, 1646, 1617, 1566. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.27 (t, *J* = 8.0 Hz, 3H, OCH$_2$C*H*$_3$), 2.32 (s, 3H, CH_3), 4.22 (q, *J* = 8.0 Hz, 2H, OC*H*$_2$CH$_3$), 5.62 (s, 1H, CH), 6.58 (s, 2H, NH_2), 6.93 (t, *J* = 8.0 Hz, 1H, ArH), 7.23 (t, *J* = 8.0 Hz, 2H, ArH), 7.60 (d, *J* = 8.0 Hz, 2H, ArH), 9.22 (br s, 1H, NH), 9.70 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 11.7, 14.2, 60.4, 84.0, 118.0, 121.6, 128.5, 140.5, 148.2, 155.9, 156.4, 161.8, 165.5. MS (EI): m/z (%) 362 [M^+, (11)], 345 (32), 253 (100), 225 (50), 185 (83), 119 (56). Anal.: calcd. for $C_{16}H_{18}N_4O_4S$ (362.40): C, 53.03; H, 5.01; N, 15.46. Found: C, 52.90; H, 5.08; N, 15.59.

Ethyl 2-[2-(4-chloroanilino)-2-oxoethylidene]-3-[(methoxycarbonyl)amino]-4-methyl-2,3-dihydro-1,3-thiazole-5-carboxylate (3f). Yield: 333.6 mg (81%). Light yellow powder, mp 204-205 °C (dec.), (from EtOH). IR (Nujol, cm^{-1}) ν_{max} 3344, 3316, 3281, 1730, 1706, 1600, 1542. ^1H NMR (400 MHz, DMSO-d_6) δ: 1.27 (t, J = 8.0 Hz, 3H, OCH_2CH_3), 2.32 (s, 3H, CH_3), 3.76 (s, 3H, OCH_3), 4.23 (q, J = 8.0 Hz, 2H, OCH_2CH_3), 5.56 (s, 1H, CH), 7.29 (t, J = 8.0 Hz, 2H, ArH), 7.61 (d, J = 8.0 Hz, 2H, ArH), 9.81 (s, 1H, NH), 10.87 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 11.5, 14.2, 53.3, 60.7, 83.8, 102.2, 119.6, 125.2, 128.5, 139.2, 147.1, 154.9, 155.8, 161.5, 165.3. MS (EI): m/z (%) 412 [M^+, (2)], 369 (2), 336 (4), 288 (100), 260 (27), 185 (16), 153 (6). Anal.: calcd. for $C_{17}H_{18}ClN_3O_5S$ (411.86): C, 49.58; H, 4.41; N, 10.20. Found: C, 49.73; H, 4.33; N, 10.12.

2-[2-(Diethylamino)-2-oxoethylidene]-*N*,*N*,4-trimethyl-3-phenyl-2,3-dihydrothiazole-5-carboxamide (4a) Yield: 255.2 mg (71%). Colourless crystals, mp:168-170 °C (from EtOAc/cyclohexane). IR (Nujol, cm^{-1}) ν_{max} 3057, 1617, 1609, 1584. ^1H NMR (400 MHz, DMSO-d_6) δ: 0.81-0.97 (m, 6H, 2 x NCH_2CH_3), 1.77 (s, 3H, CH_3), 2.86-3.22 (m, 10H, 2 x NCH_2CH_3 and $N(CH_3)_2$), 4.75 (s, 1H, CH), 7.44-7.45 (m, 2H, ArH), 7.54-7.65 (m, 3H, ArH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 13.5, 13.8, 36.7, 79.4, 108.8, 128.5, 129.5, 130.3, 136.0, 137.2, 159.9, 163.6, 165.8. MS (EI): m/z (%) 359 [M^+, (62)], 315 (7), 287 (82), 260 (100), 216 (22). Anal.: calcd. for $C_{19}H_{25}N_3O_2S$ (359.49): C, 63.48; H, 7.01; N, 11.69. Found: C, 63.66; H, 6.94; N, 11.57.

***N*,*N*,4-trimethyl-2-[2-oxo-2-(phenylamino)ethylidene]-3-phenyl-2,3-dihydrothiazole-5-carboxamide (4b)** Yield: 318.7 mg (84%). Yellow powder, mp: 237-239 °C (from EtOH). IR (Nujol, cm^{-1}) ν_{max} 3288, 3061, 1639, 1613, 1529. ^1H NMR (400 MHz, DMSO-d_6) δ: 1.78 (s, 3H, CH_3), 3.02 (s, 6H, $N(CH_3)_2$), 4.92 (s, 1H, CH), 6.87 (t, J = 8.0 Hz, 1H, ArH), 7.18 (t, J = 8.0 Hz, 2H, ArH), 7.50-7.68 (m, 7H, ArH), 9.28 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 13.5, 36.7, 83.1, 109.0, 117.7, 121.1, 128.3, 128.6, 129.5, 130.4, 136.2, 137.1, 140.6, 158.8, 163.4, 165.4. MS (EI): m/z (%) 379 [M^+, (16)], 287 (100), 242 (10), 214 (16). Anal.: calcd. for $C_{21}H_{21}N_3O_2S$ (379.48): C, 66.47; H, 5.58; N, 11.07. Found: C, 66.60; H, 5.46; N, 11.16.

2-[2-(Diethylamino)-2-oxoethylidene]-4-methyl-3-phenyl-2,3-dihydrothiazole-5-carboxamide (4c) Yield: 212.1 mg (64%). Colourless scales, mp: 211-214 °C (from EtOH). IR (Nujol, cm^{-1}) ν_{max} 3382, 3323, 3276, 3187, 1653, 1612, 1522. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.77-1.00 (m, 6H, 2 x NCH_2CH_3), 2.06 (s, 3H, CH_3), 2.86-3.23 (m, 4H, 2 x NCH_2CH_3), 4.73 (s, 1H, CH), 7.21 (s, 2H, NH_2), 7.40 (d, J = 8.0 Hz, 2H, ArH), 7.57-7.65 (m, 3H, ArH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 13.4, 13.8, 80.0, 108.6, 128.5, 129.6, 130.3, 137.1, 140.9, 159.1, 163.5, 165.7. MS (EI): m/z (%) 331 [M^+, (43)], 259 (75), 232 (100), 214 (20), 187 (5). Anal.: calcd. for $C_{17}H_{21}N_3O_2S$ (331.43): C, 61.61; H, 6.39; N, 12.68. Found: C, 61.79; H, 6.31; N, 12.55.

General procedure for the synthesis of derivatives 6a-g: To a magnetically stirred solution of ATAs **5a-c** (1 mmol) in THF (5 mL), the appropriate DD **1a, f-i** (1 mmol) was added at room temperature. After the disappearance of the reagents (1-8 h) (TLC check), the reaction was left at room temperature overnight for the complete evolution of the intermediate to the final product **6** (18-20 h). Then, the solvent was removed *in vacuo*. In some cases, solid derivatives **6** were obtained by crystallization from opportune solvent or solvent mixtures. In other cases, a chromatographic purification (cyclohexane/ethyl acetate mixtures) followed by crystallization from appropriate solvents was necessary.

Ethyl 3-[(methoxycarbonyl)amino]-4-methyl-2-(-5-oxo-3-phenyl-4,5-dihydro-4-isoxazolyliden)-2,3-dihydro-1,3-thiazole-5-carboxylate (6a). Yield: 318.7 mg (79%). Light yellow needles, mp: 190-193 °C (dec.), (from EtOH). IR (Nujol, cm^{-1}) ν_{max} 3161, 1748, 1702, 1669, 1508. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.31, (t, J = 8.0 Hz, 3H, OCH_2CH_3), 2.63 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 4.32 (q, J = 8.0 Hz, 2H, OCH_2CH_3), 7.49-7.55 (m, 5H, ArH), 11.77 (br s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.7, 14.1, 54.2, 62.5, 84.3, 114.1, 127.8, 128.9, 129.2, 130.8, 149.4, 156.0, 159.4, 162.2, 164.6, 172.1. MS (EI): m/z (%) 403 [M^+, (100)], 371 (25), 299 (17), 272 (6), 257 (8). Anal.: calcd. for $C_{18}H_{17}N_3O_6S$ (403.41): C, 53.59; H, 4.25; N, 10.42. Found: C, 53.43; H, 4.18; N, 10.54.

Methyl 3-[(methoxycarbonyl)amino]-4-methyl-2-(-5-oxo-3-phenyl-4,5-dihydro-4-isoxazolyliden)-2,3-dihydro-1,3-thiazole-5-carboxylate (6b). Yield: 284.2 mg (73%). Light yellow powder, mp: 163-165 °C (dec.), (from EtOAc-cyclohexane). IR (Nujol, cm^{-1}) ν_{max} 3187, 1753, 1733, 1700, 1563. ^1H NMR (400 MHz, $CDCl_3$) δ: 2.64 (s, 3H, CH_3), 3.85 and 3.86 (2s, 6H, 2 x OCH_3), 7.50-7.56 (m, 5H, ArH), 11.79 (br s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.7, 52.9, 54.3, 84.3, 113.4, 127.7, 128.9, 129.2, 130.8, 149.8, 156.0, 159.8, 162.1, 164.5, 172.1. MS (EI): m/z (%) 398 [M^+, (100)], 357 (22), 313 (12), 299 (7). Anal.: calcd. for $C_{17}H_{15}N_3O_6S$ (389.38): C, 52.44; H, 3.88; N, 10.79. Found: C, 52.55; H, 3.96; N, 10.92.

Methyl 3-[(*tert*-butoxyxycarbonyl)amino]-4-methyl-2-(-5-oxo-3-phenyl-4,5-dihydro-4-isoxazolyliden)-2,3-dihydro-1,3-thiazole-5-carboxylate (6c). Yield: 314.9 mg (73%). Light yellow powder, mp: 95-97 °C, (from Et_2O-light petroleum ether). IR (Nujol, cm^{-1}) ν_{max} 3279, 1750, 1731, 1701, 1669, 1509. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.46 (s, 9H, OBu^t), 2.62 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 7.45-7.55 (m, 5H, ArH), 11.18 (br s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.7, 27.8, 52.9, 83.9, 84.5, 113.2, 127.8, 128.7, 129.2, 130.7, 150.1, 154.4, 159.8, 162.1, 165.0 171.8. MS (EI): m/z (%) 431 [M^+, (21)], 375 (100), 331 (32), 313 (26), 272 (11). Anal.: calcd. for $C_{20}H_{21}N_3O_6S$ (431.46): C, 55.67; H, 4.91; N, 9.74. Found: C, 55.53; H, 5.00; N, 9.85.

Ethyl 3-[(methoxycarbonyl)amino]-4-methyl-2-[3-(4-nitrophenyl)-5-oxo-4,5-dihydro-4-isoxazolyliden]-2,3-dihydro-1,3-thiazole-5-carboxylate (6d). Yield: 304.9 mg (68%). Pale yellow crystals, mp: 165-167 °C (from MeOH). IR (Nujol, cm^{-1}) ν_{max} 3173, 3130, 1760, 1719, 1667, 1523. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.32 (t, J = 8.0 Hz, 3H, OCH_2CH_3), 2.66 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 4.29-4.37 (m, 2H, OCH_2CH_3), 7.70 (d, J = 8.0 Hz, 2H, ArH), 8.35 (d, J = 8.0 Hz, 2H, ArH), 11.53 (br s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.8, 14.1, 54.4, 62.8, 83.3, 114.5, 124.3, 129.9, 134.2, 149.2, 149.9, 155.8, 159.0, 160.1, 164.2, 171.9. MS (EI): m/z (%) 448 [M^+, (100)], 416 (22), 388 (2), 344 (6). Anal.: calcd. for $C_{18}H_{16}N_4O_8S$ (448.41): C, 48.21; H, 3.60; N, 12.49. Found: C, 48.31; H, 3.69; N,12.61.

Methyl 3-[(methoxycarbonyl)amino]-4-methyl-2-[3-(4-nitrophenyl)-5-oxo-4,5-dihydro-4-isoxazolyliden]-2,3-dihydro-1,3-thiazole-5-carboxylate (6e). Yield: 312.7 mg (72%). White powder, mp: 185-188 °C (from EtOAc). IR (Nujol, cm^{-1}) ν_{max} 3237, 3080, 1759, 1730, 1668, 1517. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.68 (s, 3H, CH_3), 3.87 and 3.88 (2s, 6H, 2 x OCH_3), 7.71 (d, J = 8.0 Hz, 2H, ArH), 8.37 (d, J = 8.0 Hz, 2H, ArH), 11.56 (br s 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.8, 53.2, 54.4, 83.4, 113.8, 124.3, 129.9, 134.2, 149.3, 150.3, 155.8, 159.4, 160.1, 164.2, 171.9. MS (EI): m/z (%) 434 [M^+, (100)], 402 (23), 358 (9). Anal.: calcd. for $C_{17}H_{14}N_4O_8S$ (434.38): C, 47.01; H, 3.25; N, 12.90. Found: C, 46.87; H, 3.32; N, 12.81.

Methyl 3-[(benzyloxycarbonyl)amino]-4-methyl-2-[3-(4-nitrophenyl)-5-oxo-4,5-dihydro-4-isoxazolyliden]-2,3-dihydro-1,3-thiazole-5-carboxylate (6f). Yield: 316.5 mg (62%). Colourless crystals, mp: 208-210 °C (from EtOAc). IR (Nujol, cm^{-1}) ν_{max} 3168, 1750, 1733, 1704, 1669, 1523. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.36 (s, 3H, CH_3), 3.87 (s, 3H, OCH_3), 4.76 (d, J = 12.0 Hz, 1H, CH_aCH$_b$Ph), 5.01 (d, J = 12.0 Hz, 1H CH$_a$CH_bPh), 7.20-7.27 (m, 2H, ArH), 7.30-7.38 (m, 3H, ArH), 7.70 (d, J = 8.0 Hz, 2H, ArH), 8.20 (d, J = 8.0 Hz, 2H, ArH), 10.79 (br s 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 11.5, 53.0, 68.1, 84.6, 110.7, 123.5, 128.2, 128.4, 128.5, 129.5, 134.5, 138.7, 147.5, 148.4, 153.4, 157.2, 160.3, 163.0, 173.3. MS (EI): m/z (%) 510 [M^+, (100)], 402 (12), 361 (11), 345 (22), 317 (40), 302 (9). Anal.: calcd. for $C_{23}H_{18}N_4O_8S$ (510.48): C, 54.12; H, 3.55; N, 10.98. Found: C, 54.25; H, 3.60; N,10.83.

Methyl 3-[(*tert*-buthoxycarbonyl)amino]-4-ethyl-2-[3-(4-nitrophenyl)-5-oxo-1-phenyl-4,5-dihydro-1*H*-4-pyrazolyliden]-2,3-dihydro-1,3-thiazole-5-carboxylate (6g). Yield: 389.7 mg (85%). Yellow powder, mp: 142-144 °C (dec.), (from $CHCl_3$-cyclohexane). IR (Nujol, cm^{-1}) ν_{max} 3193, 1740, 1722, 1704, 1610, 1592. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.26 (t, J = 8.0 Hz, 3H, CH_2CH_3), 1.37 (s, 9H, OBu^t) 2.46 (s, 3H, CH_3), 2.80-2.89 (m, 1H, CH_aCH$_b$CH$_3$), 3.32-3.41 (m, 1H, CH$_a$CH_bCH$_3$), 3.93 (s, 3H, OCH_3), 7.19 (t, J = 8.0 Hz, 1H, ArH), 7.41 (t, J = 8.0 Hz, 2H, ArH), 7.96 (d, J = 8.0 Hz, 2H, ArH), 12.54 (br s 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.4, 15.6, 20.2,

27.9, 52.8, 83.5, 95.3, 111.1, 120.0, 124.8, 128.7, 138.8, 146.7, 155.8, 160.1, 161.0, 163.5. MS (EI): m/z (%) 458 [M^+, (36)], 402 (100), 358 (58), 343 (36), 314 (3). Anal.: calcd. for $C_{22}H_{26}N_4O_5S$ (458.53): C, 57.63; H, 5.72; N, 12.22. Found: C, 57.84; H, 5.61; N, 12.16.

Acknowledgment

We gratefully acknowledge the financial support from the University of Urbino "Carlo Bo".

Notes

The authors declare no competing financial interest.

Supporting Information

Characterization data, X-ray crystallography data (**6d**), and ^{1}H and ^{13}C spectra for thiazolylidene derivatives **3a-f**, **4a-c** and **6a-g**. This material is available free of charge *via* the Internet at http://pubs.acs.org.

References

(1) Tietze, L. F., Brasche, G., Gericke, K. M., in *Domino Reactions in Organic Synthesis* Eds.; Wiley-VHC, Weinheim, Germany, 2006. (b) Pellisier, H. *Chem. Rev.* **2013**, *113*, 442.

(2) (a) Altintop, M. D.; Kaplancikli, Z. A.; Ciftci, G. A. Demirel, R. *Eur. J. Med. Chem*. **2014**, *74*, 264. (b) Faghih, R.; Gfesser, G. A.; Lynch, C. L.; Gopalakrishnan, M.; Gopalakrishnan, S.; Malysz, J.; Gubbins, E. J.; El Kouhen, R.; Li, J.; Sarris, K. A.; et al PCT Int. Appl. (2008), WO 2008002956 A2 20080103. (c) Hassanabadi, A. *J. Chem. Res*. **2013**, *37*, 331.

(3) (a) Carroll, W. A.; Dart, M. J.; Kolasa, T.; Meyer, M. D.; Patel, M. V.; Wang, X.-Q. (Abbott Laboratories), WO 2008063781, 2008. (b) Florjancic, A. S.; Dart, M. J.; Ryther, K. B.; Arturo, P.-M.; Carroll, W. A.; Patel, M. V.; Rosemarie, T. K.; Li, T.-M.; Teodozyj, K.; Gallagher, M. E.; Sridhar, P.; Frost, J. M.; Nelson D. W. (Abbott Laboratories), WO 2009067613, 2010.

(4) Guo, W.-S.; Wen, Li-R.; Li, M. *Org. Biomol. Chem*. **2014**, *13*, 1942.

(5) Bogdanowicz-Szwed, K.; Grochowski, J.; Krasodomoska, M.; Serda, P. *Monatsh*. *Chem*. **2004**, *135*, 201.

(6) (a) Verma, G. K.; Shukla, G; Nagaraju, A.; Srivastava, A.; Raghuvanshi, K.; Singh, M. S. *RSC Adv.* **2014**, *4*, 11640. (b) Shukla, G.; Verma, G. K.; Nagaraju, A.; Verma, R. K.; Raghuvanshi, K.; Singh, M. S. *RSC Adv.* **2013**, *3*, 13811.

(7) Wen, L.-R.; Men, L.-B.; He, T.; Ji, G.-J; Li, M. *Chem. Eur. J*. **2014**, *20*, 5028.

(8) For a review on the synthesis and chemistry of DDs see: (a) Attanasi, O. A.; De Crescentini, L.; Favi, G.; Filippone, P.; Mantellini. F.; Perrulli F. R.; Santeusanio, S. *Eur. J. Org. Chem*., **2009**, 3109 and reference cited therein; (b) Attanasi, O. A.; De Crescentini, L.; Filippone, P.; Mantellini, F.; Santeusanio, S. ARKIVOC 2002, ((xi)), 274 and references cited therein.

(9) (a) Attanasi, O. A.; Filippone, P.; Foresti, E.; Guidi, B.; Santeusanio, S. *Tetrahedron*, **1999**, *55*, 13423. (b) Attanasi, O. A.; Carvoli, G.; Filippone, P.; Perrulli, F. R.; Santeusanio, S. *Synlett*, **2004**, *9*, 1643. (c) Attanasi, O. A.; Favi, G.; Filippone, P.; Perrulli, F. R.; Santeusanio, S. *Synlett*, **2010**, *12*, 1859. (d) Attanasi, O. A.; De Crescentini, L.; Favi, G.; Filippone, P.; Lillini, S.; Mantellini, F.; Santeusanio, S. *Org. Lett.*, **2005**, *7*, 2469. (e) Attanasi, O. A.; Berretta, S.; De Crescentini, L.; Favi, G.; Filippone, P.; Giorgi, G.; Lillini, S.; Mantellini, F. *Tetrahedron Lett.*, **2007**, *48*, 2449. (f) Attanasi, O. A.; Bartoccini, S.; Favi, G.; Giorgi, G.; Perrulli, F. R.; Santeusanio, S. *J. Org. Chem.,* **2012**, *77*, 1161.

(10) For the synthesis of **2a-c** see: Huang, P.; Xiang, D.; Zhou, Y.; Liang, Y.; Na, T.; Dong, D. *Synthesis*, **2009**, 1797.

(11) All tentative to isolate the hydrazone intemediate **I** by crystallization or chromatographic methods failed due to its rapid transformation.

(12) For the synthesis of **5a-c** see: El-Desoky, S. I.; Etman, H. A.; Bondock, S. B.; Fadda, A. A.; Metwally, M. A. *Sulfur Letters*, **2002**, *25*, 199.

(13) Crystallographic data (excluding structure factors) for the structure of **6d** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1526978. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; (fax: + 44 (0) 1223 336 033; or e-mail: deposit@ccdc.cam.ac.uk).

(14) (a) Sommer, S. *Tetrahedron Lett.* **1977**, *18*, 117. (b) Attanasi, O. A.; Filippone, P.; Mei, A.; Santeusanio, S. *Synthesis* **1984**, 671.