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Communication

Sequential MCR *via* Staudinger/aza-Wittig *versus* cycloaddition reaction to access diversely functionalized 1-amino-1*H*-imidazole-2(3*H*)-thiones

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Abstract: A Multicomponent Reaction (MCR) strategy, alternative to the known cycloaddition reaction, towards variously substituted 1-amino-1*H*-imidazole-2(3*H*)-thione derivatives has been successfully developed. The novel approach involves α-halohydrazones whose azidation process followed by tandem Staudinger/aza-Wittig reaction with CS_2 in a sequential MCR regioselectively leads to the target compounds avoiding the formation of the regioisomer iminothiazoline heterocycle. The approach can be applied to a range of differently substituted α-halohydrazones bearing also electron-withdrawing groups confirming the wide scope and the substituent tolerance of the process for the synthesis of the target compounds. Interestingly, the concurrent presence of reactive functionalities in the scaffolds so obtained, ensures postmodifications in view of *N*-bridgedheaded heterobicyclic structures.

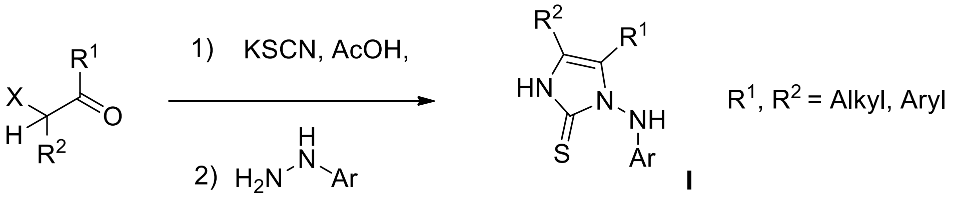
Keywords: multicomponent reaction; α-halohydrazones; Staudinger reaction; aza-Wittig; 1*H*-imidazole-2(3*H*)-thione; 2*H*-imidazo[2,1-*b*][1,3,4]thiadiazine.

1. Introduction

Imidazoles belong to an important class of heterocyclic compounds that plays crucial role in various biochemical processes [1]. A lot of imidazole-based molecules have been shown bioactivities, [2] such as antifungal, antiinflammatory, antihystamine, antihelmintic, analgesic, antineoplastic, antihypertensive activity [3-5].

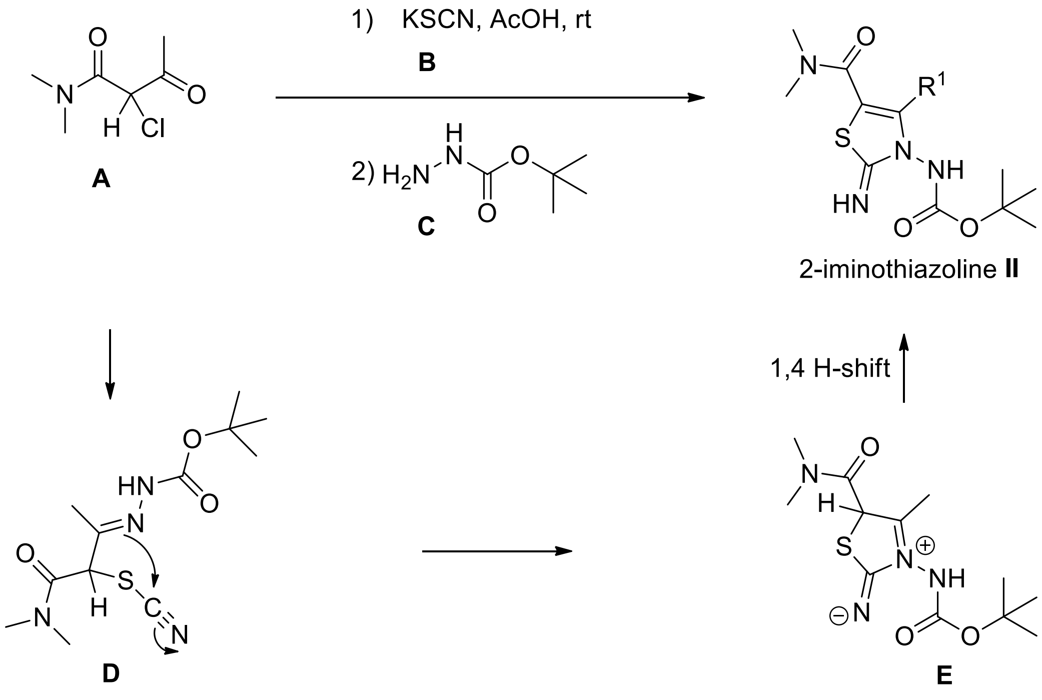
Among imidazole derivatives, imidazole-2-thiones have been associated to a special class of biologically relevant thiourea derivatives [6] endowed with antithyroid [7], antiproliferative [8], MPP (Matrix MetalloProteinases) inhibitory [9] property and can be used as building blocks for the synthesis of *N*-aminoimidazole with antiretroviral activity [10].

To date, the most widespread method used for the synthesis of *N*-substituted 1-amino-1*H*-imidazol-2(3*H*)-thiones can be referred to the Schantl's protocol which consists in reacting α-haloketones with potassium thiocyanate and monosubstituted arylhydrazines in weak acidic medium (Scheme 1) [11]. This multistep reaction is considered to proceed *via* the formation of conjugated azoalkenes, derived from α-thiocyanatohydrazones **D** (Scheme 2), and dipolarophile isothiocyanic acid intermediate that in turn undergo a [3+2] cycloaddition reaction providing substituted 1-arylamino-1*H*-imidazole-2(3*H*)-thione **I** scaffolds [12].



Scheme 1 Schantl's protocol for the synthesis of *N*-substituted 1-amino-1*H*-imidazole-2(3*H*)-thione derivatives **I**.

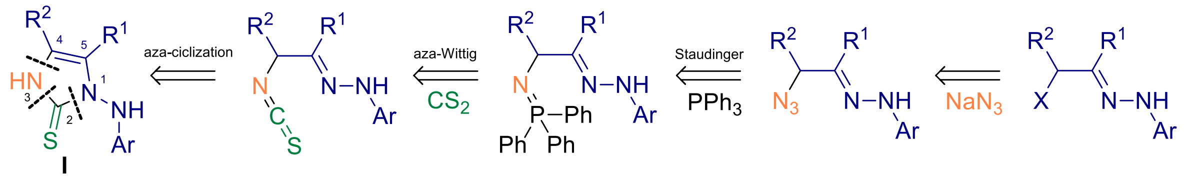
Even if this method appears robust, it seems to suffer of some limitations in terms of insertion of electron-withdrawing groups placed on the *α*-halohydrazone precursors of conjugated azoalkene intermediates. In this regard, for our research purposes, we tried to apply the Schantl's method reacting 2-chloro-*N*,*N*-dimethyl-3-oxobutanamide (**A**), potassiun thiocyanate (**B**) and *tert*-butyl hydrazinecarboxylate (**C**) in acetic acid to obtain the corresponding *N*-substituted 1-amino-1*H*-imidazole-2(3*H*)-thione derivative **I** but without success. As shown in Scheme 2, instead of the cycloaddition, a 5-exo-dig cyclization reaction leading to 2-iminothiazole **II** took place. This evidence is in agreement with the result obtained by Lagoja and coworkers where a pathway involving the key *α*-thiocyanatohydrazone intermediate **D** is invoked [10].



Scheme 2. Pathway for the formation of 2-iminothiazoline heterocycle **II**.

The structure of the iminothiazoline **II** was confirmed by comparison of the spectral data of the same compound obtained by means of a different procedure previously described by some of us that foresees the conjugated hydrothiocyanation of the pertinent conjugated azoalkene in acidic medium followed by intramolecular cyclization [13].

Inspired by our previous experience [14], and in order to perform a complete regioselective-oriented method for the desired 1-amino-1*H*-imidazole-2(3*H*)-thiones **I**, we have planned a different strategy that avoids the use of bidentate-nucleophilic reagents such as the potassium thiocyanate. In the construction of **I**, three strategic disconnections between the N1-C2, C2-N3 and N3-C4 were hypothesized (Scheme 3).

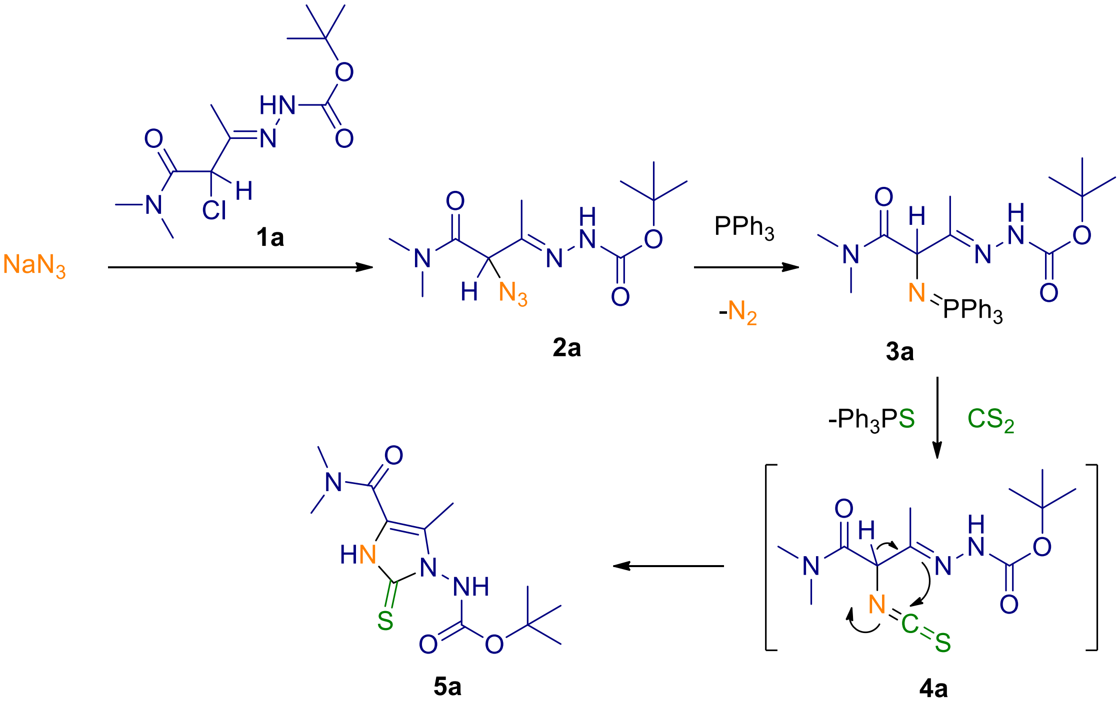


Scheme 3. Our hypothesized disconnection of 1-amino-1*H*-imidazole-2(3*H*)-thione **I** derivatives.

We reasoned that the azidation process of the pertinent α-halohydrazone derivative followed by tandem Staudinger/aza-Wittig reaction with CS_2 could have been a successful route [15].

2. Results and Discussion

To validate our hypothesis we began to explore the process step by step. Thus, α-chlorohydrazone derivative **1a** [16a] (2.0 mmol) dissolved in THF (9.0 mL) subjected to α-azidation using an ice-cooled aqueous solution of NaN_3 [17] (2.0 mmol / 1.0 mL) under magnetic stirring at room temperature. After the evaporation of the solvent and an appropriate extraction, the α-azidohydrazone derivative **2a** was obtained in 70% yield. In the next step, the addition of a stoichiometric amount of PPh_3 to **2a** (1.0 mmol) dissolved in CH_2Cl_2 (5.0 mL) furnished the iminophosphorane derivative **3a** by precipitation from the reaction medium (66%). Then, **3a** (0.65 mmol) was dissolved in 5.0 mL of THF / MeOH mixture (4:1) and treated with an excess of CS_2 at reflux to afford, after column chromatography purification, the corresponding *N*-substituted 1-amino-2,3-dihydro-1*H*-imidazole-2-thione derivative **5a** (53%) arising from intramolecular cyclization of the α-isothiocyanate hydrazone intermediate **4a** (Scheme 4).



Scheme 4. Step by step synthetic pathway for *N*-substituted 1-amino-2,3-dihydro-1*H*-imidazole-2-thione derivative **5a**.

Motivated by this result, we aimed to develop a one-pot sequential multicomponent reaction (MCR) [18] as alternative method for regioselective synthesis of a new series of imidazole-2-thiones-containing structure as suitable precursor for drug-like compounds [19].

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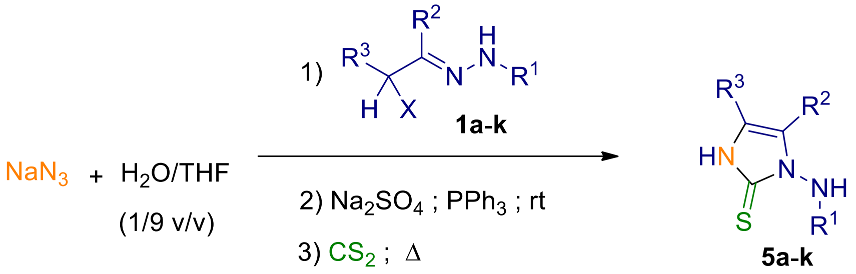
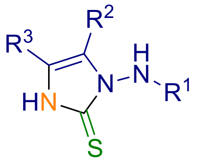
In a typical experiment, to an ice-cooled aqueous solution of NaN_3 (1.0 mmol / 0.5 mL of H_2O), α-halohydrazone derivative **1a** (1.0 mmol) solved in THF (4.5 mL) was added at room temperature under magnetic stirring. After a TLC check confirming the disappearance of **1a** and the formation of the α-azido derivative **2a** (0.5-2.0 hrs), Na_2SO_4 (0.5 g) was added in order to dehydrate the reaction environment. Then, a solution of PPh_3 (1.1 mmol) in THF (1.0 mL) and CS_2 (1.0 mL) were added in sequence and the reaction was heated to reflux. The formation of the *N*-substituted 1-amino-2,3-dihydro-1*H*-imidazole-2-thione derivative **5a** was revealed by the complete disappearance of **2a** and by the observation of $Ph_3P{=}S$ as byproduct (TLC check).

Our sequential one-pot MCR approach to *N*-substituted 1-amino-1*H*-imidazole-2(3*H*)-thiones **5a-k** (53-85%) is depicted in **Scheme 5**. It is to be noted that for **5a**, the efficiency of the reaction benefits by this latter protocol increasing the overall yield from 25% (obtained employing the step by step procedure) to 79% (Table 1). Moreover, the implemented strategy broadens the substitution patterns at the amino-N1 and at C4 of the heterocycle skeleton with electron-withdrawing groups (**5a-e**), and tolerates the aromatic (amino-N1) and aliphatic (C4) groups, as for **5j** [11c,e,f] (**Table 1**).



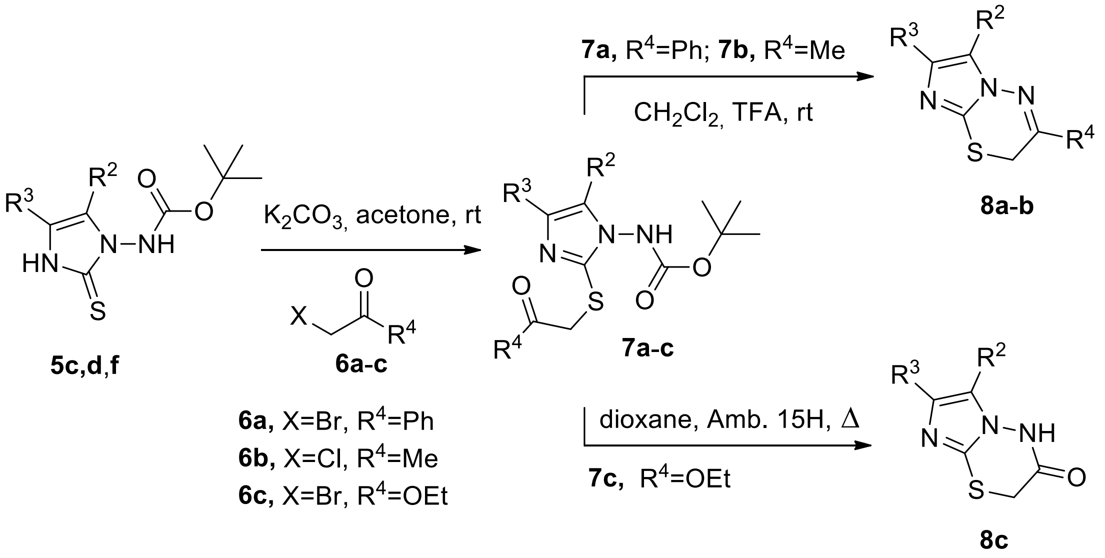
Scheme 5. New MCR method for *N*-substituted 1-amino-2,3-dihydro-1*H*-imidazole-2-thione derivatives **5a-k**

Table 1. Substrate scope of the MCRs synthetic pathway for *N*-substituted 1-amino-2,3-dihydro-1*H*-imidazole-2-thione derivatives **5a-k**

Entry		**α-Halohydrazone 1**				 **5**	***One-pot* MCR Yield (%)**[a, b]
		R^1	R^2	R^3	X		
1	**1a**	CO_2Bu^t	Me	$CON(Me)_2$	Cl	**5a**	25[a]; 79[b]
2	**1b**	CONHPh	Me	$CON(Me)_2$	Cl	**5b**	53[b]
3	**1c**	CO_2Bu^t	Me	$CON(Et)_2$	Br	**5c**	72[b]
4	**1d**	CO_2Bu^t	Me	H	Cl	**5d**	69[b]
5	**1e**	CO_2Bu^t	Me	$CONH_2$	Br	**5e**	58[b]
6	**1f**	CO_2Bu^t	Me	CONHPh	Br	**5f**	67[b]
7	**1g**	CONHPh	Me	H	Cl	**5g**	82[b]
8	**1h**	COPh	Me	H	Cl	**5h**	59[b]
9	**1i**	CONHPh	Me	Me	Cl	**5i**	85[b]
10	**1j**	$4\text{-}NO_2\text{-}Ph$	Me	Me	Cl	**5j**	84[b]
11	**1k**	CO_2Bu^t	Ph	H	Br	**5k**	66[b]

[a] Overall yield of isolated product **5a** from the step by step reaction based on **1a**; [b] Overall yield of isolated products **5a-k** from one-pot MCR based on **1a-k**.

These results not only lie in the wide scenario of the heterocyclic scaffolds obtainable through tandem Staudinger/aza-Wittig sequence [15, 20, 21], but the concurrent presence of reactive functionalities in the target compounds **5a-k** ensures postmodifications in view of heterobicyclic structures. In fact, the tautomerism thionoamide/thioloimide permits the introduction of a further element of diversity at the sulphur atom producing imidazole derivatives suitable to be combined with the useful 1-amino-Boc protected group [22] directly installed by this approach, as for **5a**, **5c-f, 5k**. Thus, as an example, **5c,d,f** (1.0 mmol) solved in acetone (10.0 mL), were reacted with 2-bromo-1-phenylethanone (**6a**) (1.0 mmol), 1-chloropropan-2-one) (**6b**) (1.0 mmol) and ethyl 2-bromoacetate (**6c**) (1.0 mmol), respectively, in the presence of K_2CO_3 (1.0 mmol). After the removal of solvent followed by extraction, the corresponding *α*-(imidazol-2-ylthio) carbonyl compounds **7a-c** were obtained as solid after column chromatography purification (84-93%) (Scheme 6). The subsequent cleavage of the Boc-protecting group under omogeneous [23] or heterogeneous acidic conditions [24] generated intermediates with a free amino function active for the intramolecular condensation with the carbonyl appendage in 2-position of the ring, affording new 2*H*-imidazo[2,1-*b*][1,3,4]thiadiazine derivatives **8a**,**b** or 2*H*-imidazo[2,1-*b*][1,3,4]thiadiazinone derivative **8c** (Scheme 6, Table 2).



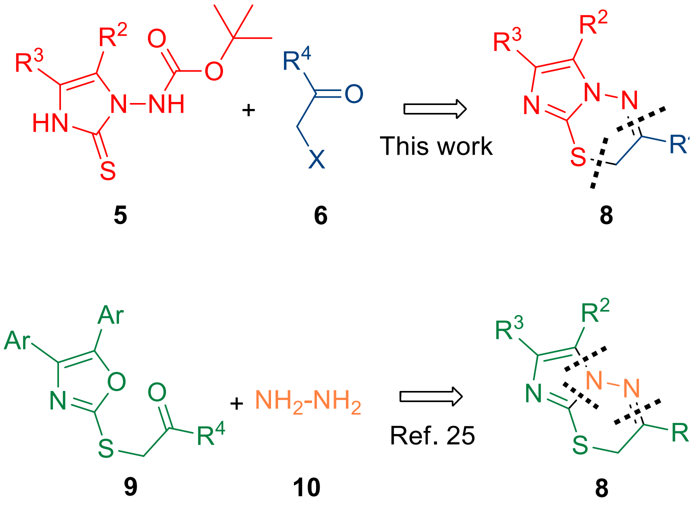
Scheme 6. Synthetic approach to 2*H*-imidazo[2,1-*b*][1,3,4]thiadiazine derivatives.

Table 2. Substrate scope of the reaction between 1-amino-2,3-dihydro-1*H*-imidazole-2-thione derivatives **5** with α-haloketones **6a,b** or α-haloester **6c**.

5			6			7	Yield (%)[a]	8	Yield (%)[b]
	R^2	R^3		X	R^4				
5c	Me	$CON(Et)_2$	**6a**	Br	Ph	**7a**	84	**8a**	82
5d	Me	H	**6b**	Cl	Me	**7b**	93	**8b**	65
5f	Me	CONHPh	**6c**	Br	OEt	**7c**	92	**8c**	74

[a]Yield of isolated product **7a-c** based on **6a-c**; [b] Yield of isolated product **8a-c** based on **7a-c**.

It is worthwhile to note that the proposed synthetic pathway can offer an alternative method for obtaining 2*H*-imidazo[2,1-*b*][1,3,4]thiadiazine derivatives **8** with respect to the ring transformation of *α*-(oxazol-2-ylthio) ketones **9** on treatment with hydrazine hydrate **10** [25], together with the possibility of wide diversification of the substituents at the different positions of the *N*-bridgeheaded heterobicyclic structures (Scheme 7).



Scheme 7. Different synthetic approaches to 2*H*-imidazo[2,1-*b*][1,3,4]thiadiazine derivatives.

3. Experimental Section

3.1. General

All the commercially available reagents and solvents were used without further purification. α-Halohydrazones **1a-k** were synthesized by known procedures [16]. Chromatographic purification of compounds was carried out on silica gel (60–200 μm). Thin-layer chromatography (TLC) analysis was performed on pre-loaded (0.25 mm) glass supported silica gel plates (Silica gel 60, F254, Merck; Darmstadt, Germany); compounds were visualized by exposure to UV light. Melting points (Mp) were determined in open capillary tubes and are uncorrected.

All ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively at 25 °C on a Bruker Ultrashield 400 spectrometer (Bruker, Billerica, MA, USA). Proton and carbon spectra were referenced internally to residual solvent signals as follows: δ = 2.50 ppm for proton (middle peak) and δ = 39.50 ppm for carbon (middle peak) in DMSO-*d*$_6$ and δ = 7.27 ppm for proton and δ = 77.00 ppm for carbon (middle peak) in $CDCl_3$. The following abbreviations are used to describe peak patterns where appropriate: s = singlet, d = doublet, t = triplet q = quartet, m = multiplet and br = broad signal. All coupling constants (J) are given in Hz. FT-IR spectra were measured as Nujol mulls using a Nicolet Impact 400 (Thermo Scientific, Madison, WI, USA). Mass spectra were obtained by ESI-MS analyses performed on Thermo Scientific LCQ Fleet Ion Trap LC/MS and Xcalibur data System. High-resolution mass spectra (HRMS) were determined with ESI resource on a Waters Micromass QTOF instrument (Waters, Milford, MA, USA). Elemental analyses were within ± 0.4 of the theoretical values (C, H, N).

3.2. *Step by step Synthetic Method for **5a***

3.2.2. Synthesis of *tert*-butyl 2-(3-azido-4-(dimethylamino)-4-oxobutan-2-ylidene)hydrazinecarboxylate (**2a**).

To the α-halohydrazone **1a** (555.5 mg, 2.0 mmol) solved in THF (9.0 mL) an ice-cooled aqueous solution (1.0 mL, T = 4 °C) of NaN_3 (2.0 mmol, 130.02 mg) was added. The reaction mixture was stirred at room temperature until the disappearance of the starting **1a** (TLC check). THF was removed under reduced pressure and the residue was diluted with water and extracted with CH_2Cl_2 (3 x 15.0 mL). The combined organic layers were dried over anhydrous $NaSO_4$ and concentrated under reduced pressure. The crude reaction was purified by crystallization from Et_2O affording the α-azido derivative **2a**. Yield 70.0% (398.0 mg) as a white solid; Mp 120-124 °C (dec); ^{1}H-NMR, 400 MHz, DMSO-*d*$_6$) δ 1.44 (s, 9H, OBu^t), 1.84 (s, 3H, CH_3), 2.86 (s, 3H, NCH_3), 2.92 (s, 3H, NCH_3), 4.99 (s, 1H, CH), 9.82 (br s, 1H, NH, D_2O exch.); ^{13}C-NMR (100 MHz, DMSO-*d*$_6$) δ 13.8, 28.0, 35.5, 36.6, 64.6, 79.5, 146.2, 152.9, 166.5; IR (Nujol, ν, cm^{-1}): 3239, 3150, 2982, 2172, 2098, 1706, 1686, 1664; MS *m*/*z* (ESI): 285.07 $(M + H)^+$; anal. calcd. for $C_{11}H_{20}N_6O_3$ (284.31): 46.47; H, 7.09; N, 29.56; found: C, 46.36; H, 7.15; N, 29.65.

3.2.3. Synthesis of *tert*-butyl 2-(4-(dimethylamino)-4-oxo-3-((triphenylphosphoranylidene)amino)butan-2-ylidene)hydrazinecarboxylate (**3a**).

1.0 Mmol of **2a** (284.31 mg) was solved in CH_2Cl_2 (5.0 mL). The reaction flask was then immersed in an ice bath (T = 0 °C), and a cooled solution of PPh_3 (262.3 mg, 1.0 mmol) in CH_2Cl_2 (1.0 mL) was added dropwise. The reaction was brought back to room temperature and stirred until the disappeareance of organic azide **2a** (monitored by TLC). The formation of phosphazene **3a** was accompanied by the development of N_2. After partial removal of the solvent under reduced pressure, **3a** was isolated by precipitation from a solution of CH_2Cl_2 / EtOAc as white powder; Yield 66% (342.3 mg); Mp 127-131 °C (dec.); ^{1}H-NMR (400 MHz, DMSO-*d*$_6$) δ 1.42 (s, 9H, OBu^t), 1.81 (s, 3H, CH_3), 2.59 (s, 3H, NCH_3), 2.73 (s, 3H, NCH_3), 4.62 (t, $J_{H\text{-}P}$ = 9.2 Hz, 1H, CH), 7.57-7.90 (m, 15H, Ar), 9.64 (s, 1H, NH, D_2O exch.) ppm; ^{13}C-NMR (100 MHz, DMSO-*d*$_6$) δ 13.0, 28.0, 35.6, 36.1, 59.3, 79.5, 120.9 ($^{1}J_{C\text{-}P}$ = 102.0 Hz), 129.7 ($^{2}J_{C\text{-}P}$ = 14.0 Hz), 133.7 ($^{3}J_{C\text{-}P}$ = 11.0 Hz), 133.8 ($^{3}J_{\text{-}CP}$ = 12.0 Hz), 134.9 ($^{4}J_{C\text{-}P}$ = 2.0

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Hz), 150.7, 167.0 ppm; IR (Nujol, ν, cm⁻¹): 3543, 3377, 3211, 1722, 1664; MS *m/z* (ESI): 519.31 $(M + H)^+$; anal. calcd. for $C_{29}H_{35}N_4O_3P$ (518.59): C, 67.17; H, 6.80; N, 10.80; found: C, 67.31; H, 6.86; N, 10.72.

3.2.4. Synthesis of *tert*-butyl (4-(dimethylcarbamoyl)-5-methyl-2-thioxo-2,3-dihydro-1*H*-imidazol-1-yl)carbamate (**5a**).

0.65 Mmol of **3a** (337.0 mg,) was solved in a mixture of THF:MeOH (4:1, 5.0 mL) heating. Then, 0.5 mL of CS_2 was added and the reaction was refluxed. The end of the reaction was defined (4.0 hrs) by the disappearance of **3a** together with the formation of $Ph_3P{=}S$ as byproduct (monitored by TLC). Removed the reaction solvents under reduced pressure, a first crop of **5a** was obtained as white powder from a solution of THF / light petroleum ether. A further amount was be gained by column chromatography eluting with CH_2Cl_2 / EtOAc mixtures. White powder from THF / light petroleum ether ; Yield 53% (103.4 mg); Mp 172-173°C (dec.); ^{1}H-NMR (400 MHz, DMSO-*d*$_6$,) δ 1.32 and 1.45 (2 s, 9H, OBu^t), 1.99 (s, 3H, CH_3), 2.94 [s, 6H, $N(CH_3)_2$], 9.69 and 10.15 (2 br s, 1H, NH, D_2O exch.), 12.50 (br s, 1H, NH, D_2O exch.) ppm; ^{13}C-NMR (100 MHz, DMSO-*d*$_6$) δ 8.9, 27.6, 27.8, 35.9, 80.8, 116.2, 128.2, 153.8, 160.2, 162.9 ppm; IR (Nujol, ν, cm⁻¹): 3188, 3115, 1741, 1645, 1607; MS *m/z* (ESI): 301.15 $(M + H)^+$; calcd. for $C_{12}H_{20}N_4O_3S$ (300.38): C, 47.98; H, 6.71; N, 18.65; found: C, 48.11; H, 6.63; N, 18.57. The partition of some signals here, as well as in the following cases, is due to the N1-amide rotameric effect [26].

4.2. *Typical MCR procedure for the synthesis of N-substituted 1-amino-1H-imidazole-2(3H)-thione derivatives* ***5a-k***.

To a round flask equipped with a magnetic stirring bar containing ice-cooled solution of NaN_3 (1.0 mmol, 65.01 mg) dissolved in 0.5 mL of H_2O, the corresponding *α*-halohydrazone **1a**-**k** (1.0 mmol) dissolved in THF (4.5 mL) was added. The mixture was stirred at room temperature until the disappearance of **1** (monitored by TLC). Upon completion, Na_2SO_4 (0.5 g), a solution of PPh_3 (1.1 mmol, 288.5 mg) in THF (1.0 mL) and CS_2 (1.0 mL) were added in sequence and the mixture was refluxed for the appropriate reaction time (3.0-20.0 hrs). The formation of the final products **5a**-**k** was revealed by the complete disappearance of the spot corresponding to the *α*-azidohydrazone **2a**-**k** as well as the detection of the byproduct $Ph_3P{=}S$. The Na_2SO_4 was filtered *in vacuo* and washed with THF (10.0 mL). The filtrate was concentrated under reduced pressure and the residue was purified by crystallization and/or by chromatography eluting with cyclohexane:EtOAc or CH_2Cl_2:EtOAc mixtures. The resulting products **5a**-**k** were isolated by crystallization from the specific solvents (see below). According to this procedure, **5a** was obtained in 79% (237.3 mg).

4.2.1 *N*,*N*,5-trimethyl-1-(3-phenylureido)-2-thioxo-2,3-dihydro-1*H*-imidazole-4-carboxamide (**5b**): Yield 53% (169.3 mg), pink powder from CH_2Cl_2 / Et_2O; Mp 247-248°C (dec.); ^{1}H-NMR (400 MHz, DMSO-*d*$_6$) δ 2.06 (s, 3H, CH_3), 2.97 [s, 6H, $N(CH_3)_2$], 7.01 (t, *J* = 8.0 Hz, 1H, Ar), 7.29 (t, *J* = 8.0 Hz, 2H, Ar), 7.46 (d, *J* = 8.0 Hz, 2H, Ar), 9.00 (s, 1H, NH, D_2O exch.), 9.33 (br s, 1H, NH, D_2O exch.), 12.56 (s, 1H, NH, D_2O exch.) ppm; ^{13}C-NMR (100 MHz, DMSO-*d*$_6$) δ 9.3, 36.8, 116.1, 118.3, 122.3, 128.7, 129.0, 139.1, 153.6, 160.3, 162.6 ppm; IR (Nujol, ν, cm−1): 3323, 3248, 3195, 3136, 1713, 1638, 1605; MS *m/z* (ESI): 320.40 $(M + H)^+$; calcd. for; $C_{14}H_{17}N_5O_2S$ (319.38): C, 52.65; H, 5.37; N, 21.93; calcd. for; $C_{14}H_{17}N_5O_2S$ (319.38): C, 52.65; H, 5.37; N, 21.93; found: C, 52.79; H, 5.44; N, 21.84.

4.2.2. *tert*-Butyl (4-(diethylcarbamoyl)-5-methyl-2-thioxo-2,3-dihydro-1*H*-imidazol-1-yl)carbamate (**5c**): Yield 72% (236.3 mg), white powder from EtOAc / THF / light petroleum ether; Mp 168-169 °C (dec.); ^{1}H-NMR (400 MHz, DMSO-*d*$_6$) δ 1.06-1.10 (m, 6H, 2xNCH$_2$*CH*$_3$), 1.32 and 1.45 (2s, 9H, OBu^t), 1.94 and 1.97 (2s, 3H, CH_3), 3.26-3.37 (m, 4H, 2xN*CH*$_2$CH$_3$), 9.68 and 10.07 (2 br s, 1H, NH, D_2O exch.), 12.49 (br s, 1H, NH, D_2O exch.) ppm; ^{13}C-NMR (100 MHz, DMSO-*d*$_6$) δ 8.6, 13.4, 27.5, 27.8, 34.8, 80.6, 117.0, 126.6, 153.8, 159.8, 162.7 ppm; IR (Nujol, ν, cm⁻¹): 3169, 3120, 1748, 1642, 1634; MS *m/z* (ESI): 329.23 $(M + H)^+$;calcd. for $C_{14}H_{24}N_4O_3S$ (328.16): C, 51.20; H, 7.37; N, 17.06; found: C, 51.09; H, 7.42; N, 16.95.

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4.2.3 *tert*-Butyl (5-methyl-2-thioxo-2,3-dihydro-1*H*-imidazol-1-yl)carbamate (**5d**): Yield 69% (158.1 mg), white powder from EtOAc / THF / light petroleum ether; Mp 168-169 °C (dec.); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.32 and 1.45 (2s, 9H, OBu^t), 1.93 (s, 3H, CH_3), 6.60 (s, 1H, CH), 9.51 and 9.94 (2 br s, 1H, NH, D_2O exch.), 11.97 (br s, 1H, NH, D_2O exch.) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6) δ 8.9, 27.9, 80.5, 108.9, 126.9, 153.9, 162.4 ppm; IR (Nujol, ν, cm^{-1}): 3271, 3144, 3098, 1744, 1732, 1640; MS *m/z* (ESI): 229.96 (M + H)$^+$; calcd. for $C_9H_{15}N_3O_2S$ (229.09): C, 47.14; H, 6.59; N, 18.33; found: C, 47.01; H, 6.65; N, 18.41.

4.2.4. *tert*-Butyl (4-carbamoyl-5-methyl-2-thioxo-2,3-dihydro-1H-imidazol-1-yl)carbamate (**5e**): Yield 58% (157.8 mg), white powder from CH_2Cl_2 / light petroleum ether; Mp 270°C (dec.); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.32 and 1.45 (2s, 9H, OBu^t), 2.23 and 2.26 (2s, 3H, CH_3), 7.23 and 7.53 (2 br s, 2H, NH_2, D_2O exch.), 9.71 and 10.17 (2s, 1H, NH, D_2O exch.), 12.42 (s, 1H, NH, D_2O exch.) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 8.9, 10.1, 27.6, 27.8, 80.9, 115.8, 133.1, 153.7, 159.6, 162.9 ppm; IR (Nujol, ν, cm^{-1}): 3395, 3354, 3182, 3137, 1754, 1717, 1676, 1594; MS *m/z* (ESI): 273.04 (M + H)$^+$; calcd. for $C_{10}H_{16}N_4O_3S$ (272.09): C, 44.10; H, 5.92; N, 20.57; found: C, 44.23; H, 5.96; N, 20.45.

4.2.5. *tert*-Butyl (5-methyl-4-(phenylcarbamoyl)-2-thioxo-2,3-dihydro-1*H*-imidazol-1-yl)carbamate (**5f**): Yield 67% (233.2 mg), white powder from EtOAc; Mp 170-171 °C (dec.); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.34 and 1.46 (2s, 9H, OBu^t), 2.28 (s, 3H, CH_3), 7.11 (t, *J* = 8.0 Hz, 1H, Ar), 7.35 (t, *J* = 8.0 Hz, 2H, Ar), 7.65 (d, *J* = 8.0 Hz, 2H, Ar), 9.68 (s, 1H, NH, D_2O exch.), 10.28 (s, 1H, NH, D_2O exch.), 12.69 (s, 1H, NH, D_2O exch.) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6) δ 9.2, 27.8, 81.0, 116.0, 119.7, 123.8, 128.8, 133.9, 138.4, 153.7, 156.3, 163.2 ppm; IR (Nujol, ν, cm^{-1}): 3375, 3243, 3066, 1752, 1659, 1630, 1598, 1545; MS *m/z* (ESI): 349.22 (M + H)$^+$; calcd. for $C_{16}H_{20}N_4O_3S$ (348.13): C, 55.16; H, 5.79; N, 16.08; found: C, 55.01; H, 5.72; N, 16.16.

4.2.6. 1-(5-Methyl-2-thioxo-2,3-dihydro-1*H*-imidazol-1-yl)-3-phenylurea (**5g**): Yield 82% (203.4 mg), white powder from THF / EtOAc; Mp 245-248 °C (dec.); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.01 (s, 3H, CH_3), 6.64 (s, 1H, CH), 6.99 (t, *J* = 8.0 Hz, 1H, Ar), 7.28 (t, *J* = 8.0 Hz, 2H, Ar), 7.46 (d, *J* = 8.0 Hz, 2H, Ar), 8.91 (s, 1H, NH, D_2O exch.), 9.25 (s, 1H, NH, D_2O exch.), 12.05 (s, 1H, NH, D_2O exch.) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6) δ 9.1, 108.8, 118.3, 122.3, 127.6, 128.8, 139,1, 153.8, 161.9 ppm; IR (Nujol, ν, cm^{-1}): 3305, 3154, 3119, 3097, 1714, 1681, 1637, 1602; MS *m/z* (ESI): 249.07 (M + H)$^+$; calcd. for $C_{11}H_{12}N_4OS$ (248.07): C, 53.21; H, 4.87; N, 22.56; found: C, 53.08; H, 4.94; N, 22.65.

4.2.7. *N*-(5-methyl-2-thioxoimidazolidin-1-yl)benzamide (**5h**): Yield 59% (137.6 mg) white powder from MeOH; Mp 240-242 °C (dec.); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.97 (s, 3H, CH_3), 6.72 (s, 1H, CH), 7.56 (t, *J* = 8.0 Hz, 2H, Ar), 7.65 (t, *J* = 8.0 Hz, 1H, Ar), 7.99 (d, *J* = 8.0 Hz, 2H, Ar), 11.44 (s, 1H, NH, D_2O exch.), 12.15 (s, 1H, NH, D_2O exch.) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6) δ 8.9, 109.3, 127.0, 127.7, 128.6, 131.5, 132.5, 162.0, 165.4 ppm; IR (Nujol, ν, cm^{-1}): 3168, 3106, 1666, 1631; MS *m/z* (ESI): 234.04 (M + H)$^+$; calcd. for $C_{11}H_{11}N_3OS$ (233.29): C, 56.63; H, 4.75; N, 18.01; found: C, 56.76; H, 4.82; N, 17.89.

4.2.8. 1-(4,5-Dimethyl-2.thioxo-2,3-dihydro-1*H*-imidazol-1-yl)-3-phenylurea (**5i**): Yield 85% (223.0 mg), white powder from THF / Et_2O; Mp 245-250 °C (dec.); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.94 (s, 3H, CH_3), 1.99 (s, 3H, CH_3), 6.99 (t, *J* = 8.0 Hz, 2H, Ar), 7.28 (t, *J* = 8.0 Hz, 1H, Ar), 7.46 (d, *J*= 8.0 Hz, 2H, Ar), 8.89 (s, 1H, NH, D_2O exch.), 9.19 (s, 1H, NH, D_2O exch.), 12.00 (s, 1H, NH, D_2O exch.) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6) δ 7.8, 8.9, 116.6, 118.3, 122.2, 122.5, 128.7, 139.1, 153.9, 160.7 ppm; IR (Nujol, ν, cm^{-1}): 3271, 3172, 3095, 1719, 1691, 1665, 1603; MS *m/z* (ESI): 263.11 (M + H)$^+$; calcd. for $C_{12}H_{14}N_4OS$ (262.33): C, 54.94; H, 5.38; N, 21.36; found: C, 54.87; H, 5.46; N, 21.23.

4.2.9. 4,5-Dimethyl-1-[(4-nitrophenyl)amino]-1*H*-imidazole-2(3*H*)-thione (**5j**): Yield 84% (222.0 mg), beige powder from THF / EtOAc / Et_2O; Mp 279-282 °C (dec.); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.90 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 6.59 (d, *J* = 8.0 Hz, 2H, Ar), 8.10 (d, *J*= 8.0 Hz, 2H, Ar), 10.09 (s, 1H, NH,

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D_2O exch.), 12.19 (s, 1H, NH, D_2O exch.) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6) δ 7.6, 9.0, 111.3, 117.8, 121.7, 125.8, 139.3, 153.0, 160.8 ppm; IR (Nujol, ν, cm^{-1}): 3199, 3094, 1673, 1594; HRMS *m*/*z* calcd. for $[M + H]^+$ $C_{11}H_{13}N_4O_2S$ 265.0759; found 265.0774.

4.2.10. *tert*-Butyl (5-phenyl-2-thioxo-2,3-dihydro-1*H*-imidazol-1-yl)carbamate (**5k**): Yield 66% (192.3 mg), light yellow powder from THF / EtOAc / light petroleum ether; Mp 172-174 °C (dec.); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.17 and 1.39 (2s, 9H, OBu^t), 7.18 (s, 1H, CH), 7.35-7.49 (m, 5H, Ar), 9.79 and 10.12 (2s, 1H, NH, D_2O exch.), 12.51 (br s, 1H, NH, D_2O exch.) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6) δ 27.5, 27.9, 80.2, 80.5, 110.7, 110.8, 126.9, 127.0, 127.7, 127.9, 128.1, 128.5, 130.6, 130.8, 153.2, 153.9, 162.0, 164.2 ppm; IR (Nujol, ν, cm^{-1}): 3275, 3120, 3093, 1726, 1618, 1600; MS *m*/*z* (ESI): 292.18 $(M + H)^+$; calcd. for $C_{14}H_{17}N_3O_2S$ (291.37); C, 57.71; H, 5.88; N, 14.42; found: C, 57.83; H, 5.82; N, 14.37.

4.3. *General procedure for the synthesis of α-(imidazol-2-ylthio) carbonyl compounds* ***7a*-*c***.

To a suspension of the *N*-Boc-protected 1-amino-1*H*-imidazole-2(3*H*)-thione derivatives **5c**,**d**,**f** (1.0 mmol) and K_2CO_3 (1.0 mmol, 138 mg) in 10.0 mL of acetone was added the corresponding *α*-halocarbonyl derivative **6a-c** (1.0 mmol). The reaction mixture was kept under magnetic stirring at room temperatures. Upon completion (monitored by TLC) the solvent was removed and the crude reaction mixture was quenched to neutrality with a solution of HCl 1N and extracted with EtOAc (30.0 mL). The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed in vacuum and the crude extract was purified by crystallization or by column chromatography eluting with cyclohexane:ethyl acetate mixtures to furnish **7a**-**c** derivatives in good yields (84-93%).

4.3.1. *tert*-Butyl (4-(diethylcarbamoyl)-5-methyl-2-((2-oxo-2-phenylethyl)thio)-1*H*-imidazol-1-yl)carbamate (**7a**): Yield 84% (375.1 mg); white solid from Et_2O; Mp 123-126 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.14-1.23 (m, 6H, 2xNCH$_2CH_3$), 1.48 (s, 9H, OBu^t), 1.98 (s, 3H, CH_3), 3.37-3.64 (m, 4H, 2xNCH_2CH$_3$), 4.50 (br s, 1H, SCH_aH$_b$), 4.69 (br s, 1H, SCH$_aH_b$), 7.46 (t, *J* = 8.0 Hz, 2H, Ar), 7.58 (t, *J* = 8.0 Hz, 1H, Ar), 7.97 (d, *J* = 8.0 Hz, 2H, Ar), 9.45 (br s, 1H, NH, D_2O exch.) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 8.7, 12.9, 14.5, 28.0, 40.6, 41.6, 43.4, 82.5, 128.4, 128.5, 128.7, 130.9, 133.7, 135.3, 135.4, 139.9, 153.8, 164.5, 193.7 ppm; IR (Nujol, ν, cm^{-1}): 3114, 3059, 1741, 1726, 1700, 1681, 1597, 1584; MS *m*/*z* (ESI): 447.35 $(M + H)^+$; calcd. for $C_{22}H_{30}N_4O_4S$ (446.56): C, 59.17; H, 6.77; N, 12.55; found: C, 59.02; H, 6.84; N, 11.67.

4.3.2. *tert*-Butyl (5-methyl-2-((2-oxopropyl)thio)-1*H*-imidazol-1-yl)carbamate (**7b**): Yield 93% (265.4 mg); ocher solid from EtOAc / cyclohexane; Mp 103-104 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.50 (s, 9H, OBu^t), 2.14 (s, 3H, CH_3), 2.24 (s, 3H, $COCH_3$), 3.81 (br s, 1H, SCH_aH$_b$), 3.94 (br s, 1H, SCH$_aH_b$), 6.77 (s, 1H, CH), 8.26 (br s, 1H, NH, D_2O exch.) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 8.9, 28.0, 28.8, 44.8, 82.8, 125.1, 131.5, 139.5, 154.1, 203.5 ppm; IR (Nujol, ν, cm−1): 3125, 1725, 1714; MS *m*/*z* (ESI): 286.17 $(M + H)^+$; calcd. for $C_{12}H_{19}N_3O_3S$ (285.36): C, 50.51; H, 6.71; N, 14.73; found: C, 50.40; H, 6.78; N, 14.86.

4.3.3. Ethyl 2-((1-((*tert*-Butoxycarbonyl)amino)-5-methyl-4-(phenylcarbamoyl)-1*H*-imidazol-2-yl)thio)acetate (**7c**): Yield 92% (399.7 mg), white solid from EtOAc / cyclohexane; Mp 134-136 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.27 (t, *J* = 8.0 Hz, 3H, OCH$_2CH_3$), 1.51 (s, 9H, OBu^t), 2.55 (s, 3H, CH_3), 3.66 (d, *J* = 16.0 Hz, 1H, SCH_aH$_b$), 3.90 (d, *J* = 16.0 Hz, 1H, SCH$_aH_b$), 4.17-4.24 (m, 2H, OCH_2CH$_3$), 7.10 (t, *J* = 8.0 Hz, 1H, Ar), 7.34 (t, *J* = 8.0 Hz, 2H, Ar), 7.67 (d, *J* = 8.0 Hz, 2H, Ar), 8.18 (br s, 1H, NH, D_2O exch.), 8.96 (s, 1H, NH, D_2O exch.) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 9.4, 14.0, 28.0, 36.7, 62.7, 83.4, 119.5, 123.8, 128.9, 129.9, 137.3, 138.0, 139.0, 153.6, 160.6, 169.9 ppm; IR (Nujol, ν, cm−1): 3315, 3182, 1733, 1647, 1601; MS *m*/*z* (ESI): 435.20 $(M + H)^+$; calcd. for $C_{20}H_{26}N_4O_5S$ (434.51): C, 55.28; H, 6.03; N, 12.89; found: C, 55.39; H, 5.97; N, 12.81.

4.4. *General procedure for the synthesis of N-bridgeheaded heterobicyclic derivatives* ***8a-c****.*

Derivative **7a,b** (1.0 mmol) was solved in 5.0 mL of a solution of trifluoroacetic acid (TFA) and CH_2Cl_2 (1:1). The reaction mixture has been left at room temperature until the disappeareance of the starting **7a**,**b** (TLC check). Then, the solvent was removed under reduced pressure and the crude reaction mixture was quenced to neutrality with a satured solution of Na_2CO_3 and extracted with EtOAc (20.0 mL x 3). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. After the removal of the solvent, the crude extract was purified by crystallization or by column chromatography eluting with cyclohexane:ethyl acetate mixtures to furnish **8a**,**b** derivatives. For obtaining **8c**, the best condition found was to treat **7c** (1.0 mmol) with Amberlyst 15H (500 mg) in refluxing dioxane (15.0 mL) for 12.0 hrs. Upon completion (monitored by TLC) the resin was filtered off in vacuo and washed with THF (20.0 mL). The filtrate was evaporated under reduced pressure and the crude reaction mixture was purified by cristallization.

4.4.1. *N*,*N*-diethyl-6-methyl-3-phenyl-2*H*-imidazo[2,1-*b*][1,3,4]thiadiazine-7-carboxamide (**8a**): Yield 82% (269.3 mg) white powder from EtOAc / cyclohexane; Mp 125-127 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.22 (t, *J* = 8.0 Hz, 6H, 2xNCH$_2$*CH*$_3$), 2.56 (s, 3H, CH_3), 3.53 (br s, 2H, N*CH*$_2$CH$_3$), 3.74 (br s, 2H, N*CH*$_2$CH$_3$), 3.97 (s, 2H, SCH_2), 7.50-7.52 (m, 3H, Ar), 7.90 (d, *J* = 8.0 Hz, 2H, Ar) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 9.7, 13.0, 14.5, 23.9, 40.3, 43.0, 127.0, 128.9, 129.7, 131.1, 131.3, 133.5, 134.2, 150.8, 164.1 ppm; IR (Nujol, ν, cm^{-1}): 1611, 1574, 1562, 1557; MS *m/z* (ESI): 329.28 (M + H)$^+$; calcd. for $C_{17}H_{20}N_4OS$ (328.43): C, 62.17; H, 6.14; N, 17.06; found: C, 62.04; H, 6.19; N, 17.15.

4.4.2. 3,6-Dimethyl-2*H*-imidazo[2,1-*b*][1,3,4]thiadiazine (**8b**): Yield 65% (108.7 mg); white needles from $CHCl_3$ / cyclohexane; Mp 57-58 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.26 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 3.42 (s, 2H, SCH_2), 6.70 (s, 1H, CH), ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 8.8, 23.5, 26.1, 123.7, 128.6, 130.1, 152.0 ppm; IR (Nujol, ν, cm−1): 1640. 1582; MS *m*/*z* (ESI): 168.06 (M + H)$^+$; calcd. for $C_7H_9N_3S$ (167.23): C, 50.27; H, 5.42; N, 25.13; found: C, 50.39; H, 5.39 N, 25.06.

4.4.3. 6-Methyl-3-oxo-*N*-phenyl-3,4-dihydro-2*H*-imidazo[2,1-*b*][1,3,4]thiadiazine-7-carboxamide (**8c**): Yield 74% (213.3 mg), light yellow powder from EtOAc / light petroleum ether; Mp 229-232 °C; ^{1}H-NMR (400 MHz, DMSO-*d*$_6$) δ 2.53 (s, 3H, CH_3), 3.81 (s, 2H, SCH_2), 7.04 (t, *J* = 8.0 Hz, 1H, Ar), 7.29 (t, *J* = 8.0 Hz, 2H, Ar), 7.81 (d, *J* = 8.0 Hz, 2H, Ar), 9.80 (s, 1H, NH, D_2O exch.), 12.27 (br s, 1H, NH, D_2O exch.) ppm; ^{13}C-NMR (100 MHz, DMSO-*d*$_6$): δ 9.2, 29.7, 119.8, 123.0, 128.3, 128.4, 130.6, 132.2, 138.8, 160.8, 164.6 ppm; IR (Nujol, ν, cm−1): 1679, 1666, 1595, 1582; MS *m/z* (ESI): 288.97 (M + H)$^+$; calcd. for $C_{13}H_{12}N_4O_2S$ (288.32): C, 54.15; H, 4.20; N, 19.43; found: C, 54.08; H, 4.27; N, 19.31.

Conclusions

In conclusion, combining sequential azidation, Staudinger and aza-Wittig reactions with CS_2 on α-halohydrazones in a one-pot protocol, variously substituted 1-amino-1*H*-imidazole-2(3*H*)-thiones are directly accessible in good yields and with complete control of regioselectivity. The method is particularly attractive and advantageous for its mild conditions, operational simplicity and its efficiency as well as its robustness (wide substrate scope and tolerance of various functional groups) and reliability. Besides, the concurrent presence of reactive appendages on the obtained scaffolds ensures postmodifications toward *N*-bridgedheaded heterobicyclic structures.

Supplementary Materials: The following are available online: procedure followed for obtaining **II**; copies of ^{1}H-NMR and ^{13}C-NMR spectra of **II** [13]; copies of ^{1}H-NMR and ^{13}C-MNR spectra of all newly synthesized compounds; copies of HMQC of compound **5a** and **8c**.

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