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Heterocycles by cascade reactions of versatile thioureido-acetamides

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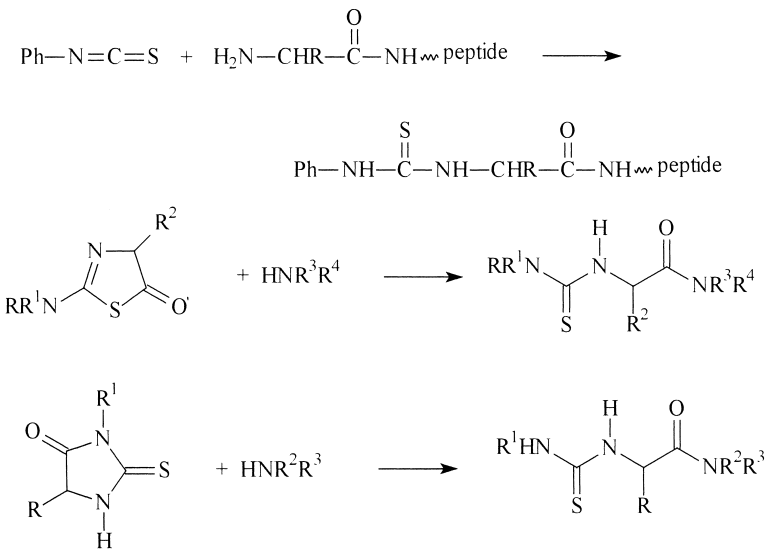
Abstract—Thioureido-acetamides (**1**) are quantitatively accessible by gas–solid reaction of amines with thiohydantoins. They are useful starting materials for various heterocyclic syntheses in one-pot cascade reactions with excellent atom economy: 2-iminothiazoles (**5**) are quantitatively formed from **1** and phenacyl bromide in the solid state. Thioparabanic acids (**9**) are easily accessible from oxalyl dichloride and **1**. Benzils react with **1** to afford functionalized 5,5-diaryl-thiohydantoins (**14**) and dimethylacetylene dicarboxylate gives 2-imino-5-methylene-thiazolidine-4-ones (**17**) and (**18**) upon reaction with **1**. The one-pot syntheses of imidazo[1,2-*c*]pyrimidines (**25**) and (**28**) from **1** with benzaldehydes and ethyl cyanoacetate or malodinitrile are benign new accesses to these important heterocycles. All product structures are determined from spectroscopic and chemical data and preferred tautomers are judged by DFT calculations at the B3LYP/6-31G* level.

1. Introduction

Thioureido-acetamides are prepared by the addition of isothiocyanates to α-aminoacid amides or to peptides in the Edman sequential analysis,[1] by ring opening of 2-amino-1,3-thiazoline-5-ones[2–4] or by ring opening of 2-thio-hydantoins.[5–7] The use of thioureido-acetamides as bactericides[8,9] and sweeteners[10] was demonstrated. We have been able to increase the yield in various instances from moderate in solution to quantitative by applying gas–solid techniques without any solvent.[7] Thus, thioureido-acetamides are now most easily available from versatile thiohydantoins and gaseous or vaporized amines without producing wastes.

We present here the synthetic use of these environmentally benign building blocks with various heterocyclization reactions (Scheme 1).



Scheme 1. Previous syntheses techniques for thioureido-acetamides.

Keywords: atom economy; benign building blocks; cascade reactions; heterocycles; neat reactions; solid-state reactions; sustainable chemistry; thioureido-acetamides.

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2. Results and discussion

2.1. Cyclization of 1 with phenacyl bromide (2)

The thiourea unit in **1** cyclocondenses with phenacyl bromide (**2**) in the solid state. The substituted 2-alkylamino-1,3-thiazolium salts **4** are obtained quantitatively. Clearly, a reaction cascade is occurring in the solid state that has ample precedence.[11] The free 2-alkylaminothiazoles **5a**, **b** or the 2-alkyliminothiazole **5′c** can be easily liberated with base. The 2-aminothiazole tautomers **5a**,**b** must be considerably more stable than their imino forms (analogs of **5′**). This is indicated by DFT model calculations at the B3LYP/6-31G* level that predict 2-methylamino-4-phenyl-1,3-imidazol by 11.61 kcal mol^{-1} more stable than its imino tautomer (Scheme 2).

2-Amino-1,3-thiazoles have a wide range of biological activities.[12,13] Recently, 2-amino-4-phenyl-1,3-thiazole derivatives were found to inhibit IL-6 secretion stimulated by parathyroid hormone (PTH) in osteoblastic MC3T3-E1 cells.[14] Thus, our waste-free access to 2-amino-1,3-thiazoles may be of pharmacological importance.

2.2. Cyclizations of 1 with oxalyl dichloride (6)

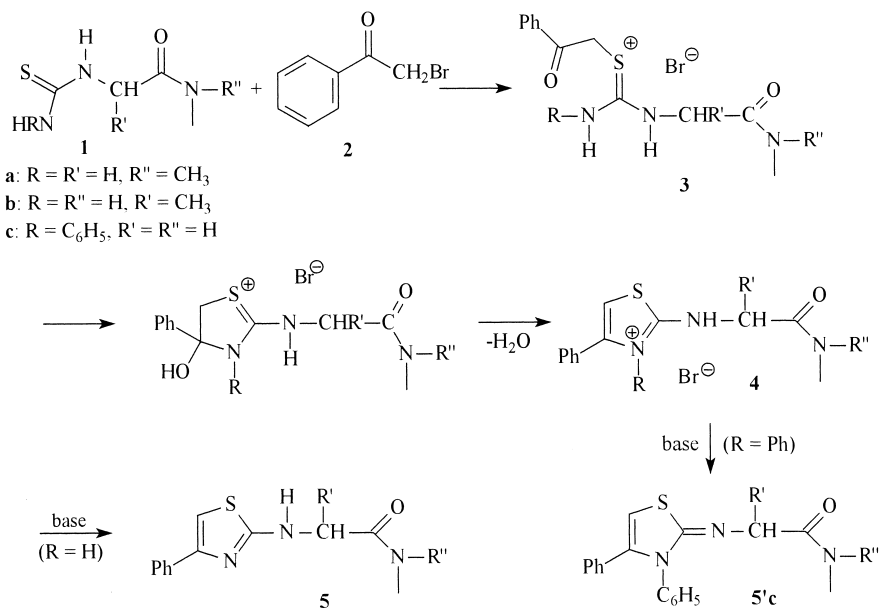
Thioureas and oxalyl dichloride (**6**) give thioparabanic acids (similar to **9**)[15–19] apparently via 2-imino-thiazolidine-4,5-dione intermediates (similar to **8**).[17] This reaction type can be successfully applied to our thioureido-dimethylacetamides **1a**,**f**,**g**. Thus, the thioparabanic acid derivatives **9a**,**f**,**g** could be synthesized with yields in the range of 80% in dry THF (−10 to 67°C). The intermediate imino-thiazolidine-dione **8** or its isomer **8″** (that could equally rearrange to give **9**) could not be detected under these conditions. It was, however, possible to stop part of the reaction of **1a** at the intermediate stage if the reaction was performed in 1,2-dichloroethane, and IR spectra showed the occurrence of two additional carbonyl peaks that disappeared upon refluxing of the mixture in ethanol to give the rearranged **9a**. Thus, the obtained product **9** must be the thermodynamically more stable isomer and clearly, density functional B3LYP/6-31G* calculations see **9a** 16.60 kcal mol^{-1} more stable than **8a**, 13.30 kcal mol^{-1} more stable than **8′a** or 16.47 kcal mol^{-1} more stable than **8″a**. Furthermore, ^{13}C NMR simulations in the Specinfo database predict the chemical shift for C-4 of **9a** (δ=154.6) with a value of 155.2, whereas the predictions for the corresponding carbonyls in **8a**, **8′a**, and **8″a** would be 174.3 (Scheme 3).

The intermediacy of **8**/**8′** could be confirmed by running these reactions solvent-free. Thus, stoichiometric mixtures of **1a** and **6** at −10°C gave crude spectra in the NMR that indicated the presence of 82% **8′a**. This product transformed into a 74% yield of **9a** upon recrystallization from ethanol. The formula **8″a** was excluded by the absence of the typical imine-NH vibration at 3280–3300 cm^{-1} in the IR spectrum. The solvent-free solid-state reaction of **1f** and **6** at −30°C in a ball-mill gave a mixture of 31% **8f** (or **8″f** ?) and 61% **9f** as detected by NMR spectroscopy. An 83% yield of **9f** was obtained upon recrystallization from ethanol. Thus, the neat stoichiometric reactions (without solvent) give mechanistic hints that cannot be obtained in solutions.

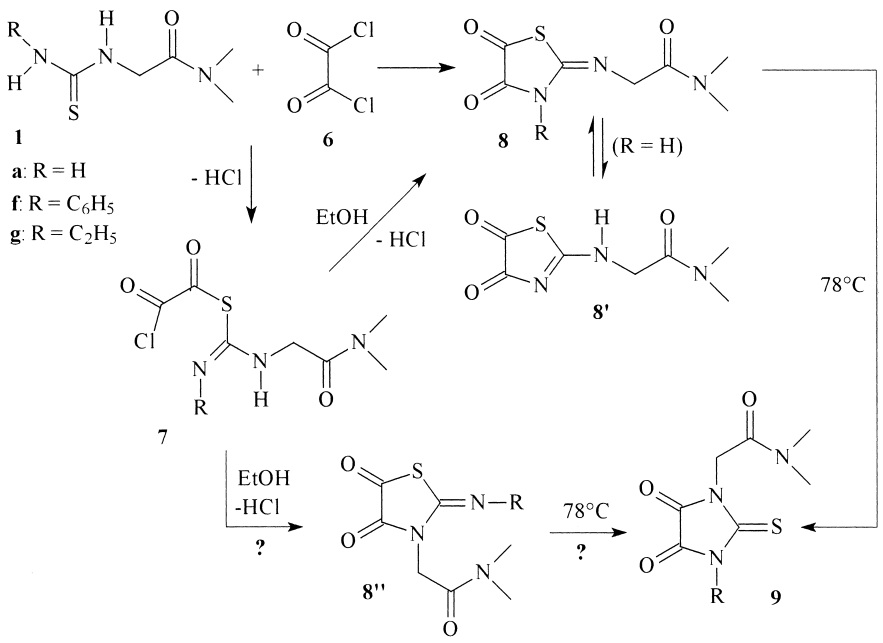
The easy access of new thioparabanic acid derivatives may be of interest as several of these are versatile starting materials for histamine blockers.[19,20]

2.3. Cyclization of 1 with benzils 10

Monosubstituted thioureas react with benzils **10** in the presence of NaOH to give 5,5-diphenyl-thiohydantoins.[21–23] This reaction type can be equally obtained with thioureido-acetamides to give the functionalized 5,5-diaryl-thiohydantoins **14**, that may be useful as precursors for 5,5-diarylhydantoins: derivatives of the antiepileptic and anti-arrhythmic drug phenytoin (5,5-diphenylhydantoin).[24,25] After boiling for 15 h in ethanol in the presence of NaOH the yields of **14a–c** were 53, 45 and 49%. Intermediates of



Scheme 2. Quantitative solid-state syntheses of 2-alkylamino-1,3-thiazolium salts, 2-aminothiazoles, and a 2-alkylimino-3*H*-thiazoline.



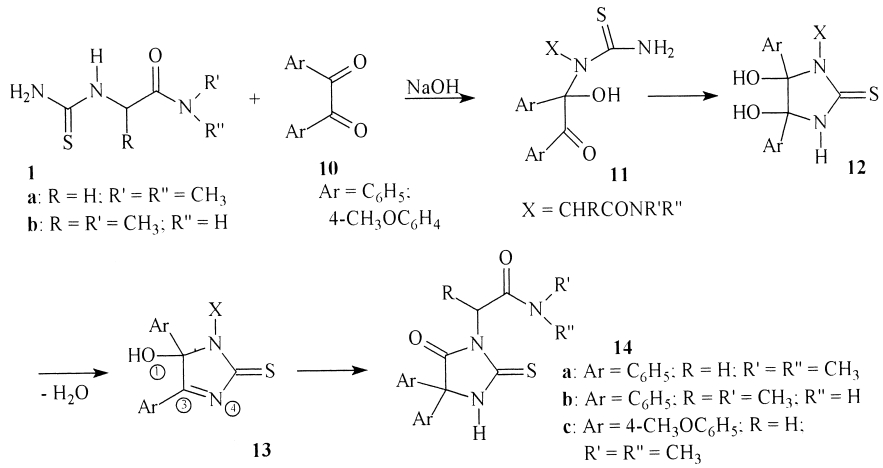
Scheme 3. Synthesis of substituted thioparabanic acids **9** with presumed reaction course.

the types **12** and **13** were isolated in related reactions of thiourea and *N*-methyl-thiourea.[23] The most likely reaction sequence via **11**–**13** may require the base in all steps including the final [1,2,3,4]-rearrangement[26] of **13** to give **14**. A pinacol rearrangement of **12** to give **14** is unlikely, as it would require acid catalysis.[26] However, similar [1,2,3,4]-rearrangements were obtained when 5-hydroxy-4,5-diaryl-1-phenyl-1,5-dihydroimidazol-2-ones were treated with KOH,[27] or when 3-hydroxy-3*H*-indoles and NaOH gave the corresponding 1,2-dihydro-3-indolones.[28] The structures of **14** were confirmed by the occurrence of the fragments $Ar_2C{=}N^+$ in the mass spectra (Scheme 4).

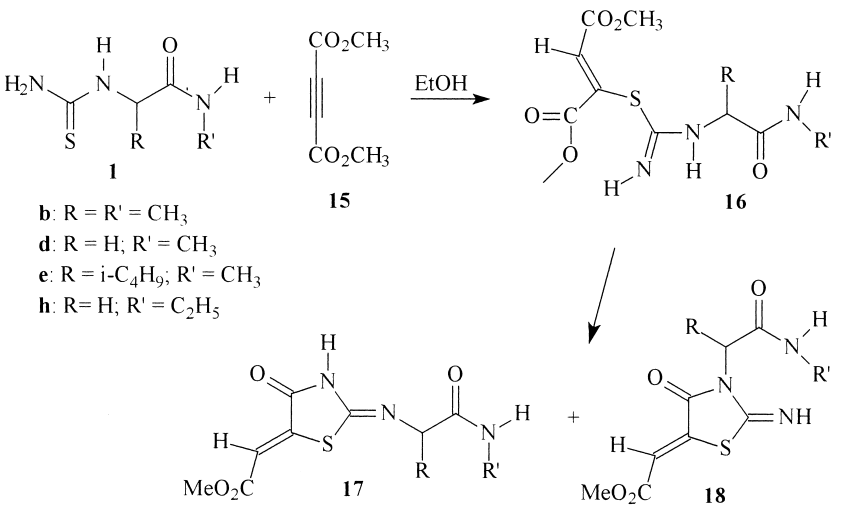
2.4. Cyclization of 1 with dimethylacetylene dicarboxylate (15)

Thioureas and dimethylacetylene dicarboxylate give 2-imino-5-methoxycarbonylmethylene-thiazolidene-4-ones (similar to **17** and **18**).[29–32] This reaction type can be equally used for the synthesis of acetamido derivatives when thioureido-acetamides are applied.

Pure racemic compounds **17b**,**e** separated after boiling in ethanol with yields of 86 and 83%. However, mixtures of the isomers **17d**,**h** and **18d**,**h** (product ratios 1.00:0.43 and 1.00:0.59) were obtained from **1d**,**h** (with R=H). Thus, an alkyl group R in intermediates **16** prevents the attack of the substituted N in the amidine unit to the ester group for steric reasons. The same reactions were performed under neat stoichiometric conditions at room temperature in a ball mill in an attempt to obtain both spectroscopic evidence for intermediates **16** and increased yields in **17**. It turned out that the ratios of **17d**,**h**/**18d**,**h** were almost reversed at the milder conditions. Furthermore, if the reaction was performed by co-grinding in a mortar and standing for 40 h (**1d**) or 17 h (**1h**) at room temperature, the olefinic ^{1}H NMR singlets of **17d**,**h**/**18d**,**h** were accompanied by additional low field singlets at 6.80 and 6.83 ppm (13 and 9%, respectively). These were lost upon workup and may thus belong to the intermediates **16d**,**h**. Unfortunately, complete spectra of the presumed intermediates could not be extracted from the ^{1}H NMR spectra due to considerable overlap of most peaks (Scheme 5).



Scheme 4. Synthesis of functionalized 5,5-diaryl-thiohydantoins.



Scheme 5. Synthesis of 2-imino-5-methoxycarbonylmethylene-thiazolidine-4-ones.

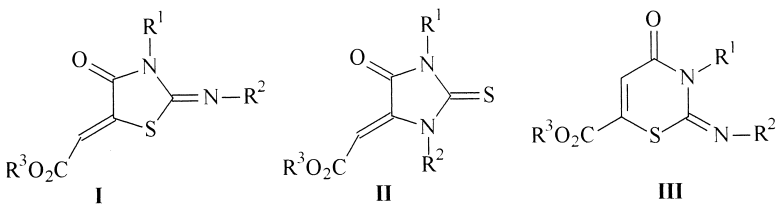
The chemical structures of **17** and **18** are derived from the analytical and spectroscopic data. Three heterocyclic structures were discussed for reactions of substituted thioureas with acetylene dicarboxylates: imino-thiazolidinones **I**,[29–32] thioxo-imidazolidinones **II**,[33] and imino-1,3-thiazidinones **III**.[34,35] X-ray analyses for the products from *N*-methyl-thiourea and *N*-thiocarbamoylpiperidine exhibited structure **I**.[36,37] As density functional theory calculations (B3LYP/6-31G*) indicated a clear energetic preference of **II** in our cases (R^1=H, R^2=$-CH_2CONH_2$, R^3=CH_3 or R^1 and R^2 interchanged), a more detailed investigation was required. Structure **III** was excluded by the ^3J heterocoupling constants found between the vinylic H and the carbonyl-C in the gated ^{13}C NMR spectra of **17h** and **18h** that were found at 4.7 and 4.8 Hz. Coupling constants of ≤1.3 Hz would be expected for structure **III**.[28] At the same time, the coupling constants confirm the *Z*-configuration of the C=C-double bond both in **I** or **II**. Suitable reference systems indicate coupling constants of 4–7.5 Hz for the *cis* and 10–14.5 Hz for the *trans* arrangement of the respective nuclei[31,38–41] (Scheme 6).

For a secure exclusion of structure **II** for the reactions of **1** with **15** the derivative **21a** was prepared on an alternate path by reaction of the isothiocyanato ester **19**[42] with glycine methylamide **20a**.[43] The spectral data of **21a** compare favorably with those of the 4-ylidene-thioxoimidazolidinones **21b**, **c** which had been confirmed by X-ray structure analyses.[42,44] They do, however, differ from those of **17d** and **18d** (Scheme 7).

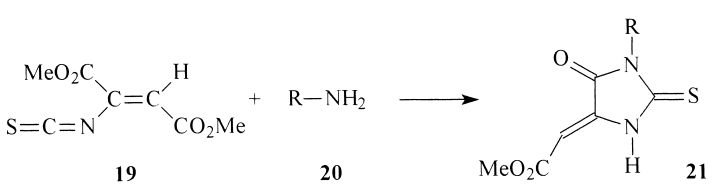
2.5. Synthesis of imidazo[1,2-*c*]pyrimidines

The reaction of benzaldehyde and ethyl cyanoacetate (or of the isolated benzylidene malonic ester nitrile (**22**) therefrom) with thiourea in the presence of a base gives 6-phenyl-4-oxo-2-thiouracil-5-nitrile (cf. **23**) in a one pot synthesis.[45,46] If this strategy is applied to thioureido-acetamides it may be expected that the intermediates cyclocondense to give imidazo[1,2-*c*]pyrimidines (Scheme 8).

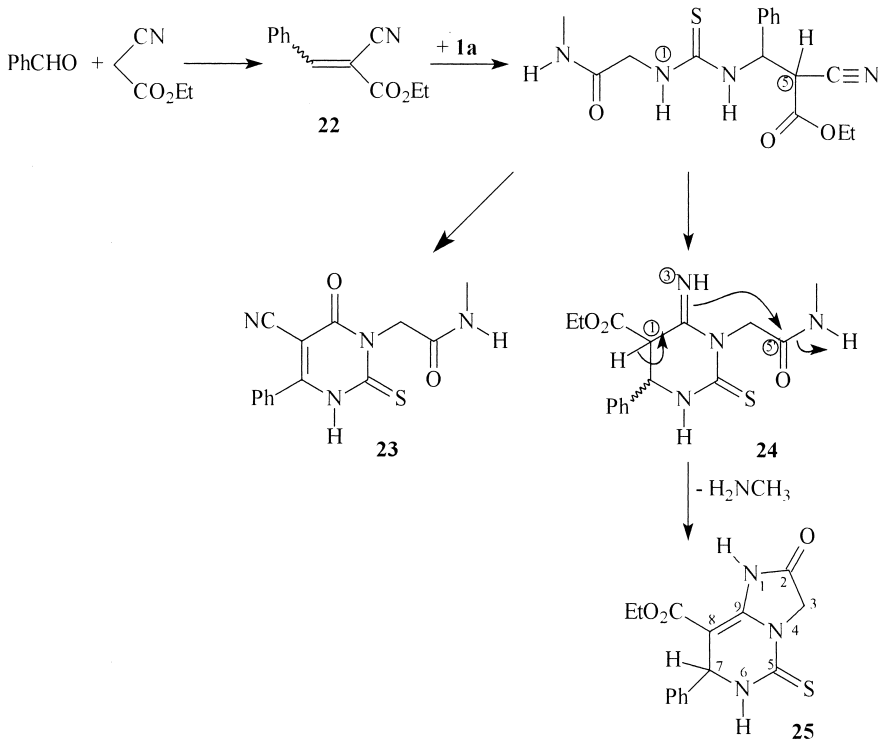
Michael addition of **1a** to the benzylidene intermediate **22** produces intermediates which can undergo



Scheme 6. Possible structures in the reaction of thioureas with acetylene dicarboxylates.



Scheme 7. Reference synthesis of 4-ylidene-thioxoimidazolidinones.

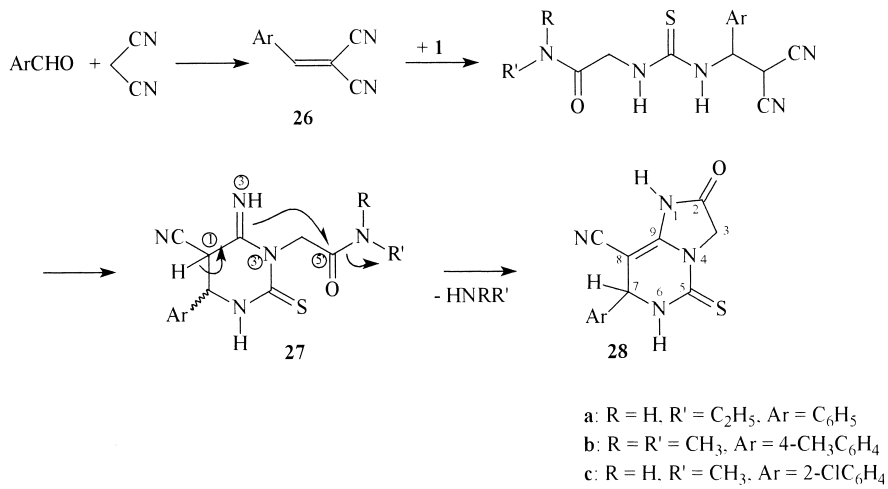


Scheme 8. One-pot synthesis of an ethoxycarbonyl imidazo[1,2-*c*]pyrimidine from benzaldehyde, ethyl cyanoacetate, and thiourea with presumed reaction course.

[1,6]-elimination to give the undesired **23** (21%) and [1,6,7]-rearrangement to give intermediate **24**. While **23** was stable under the experimental conditions, **24** underwent the cyclizing [1,2,(3)5′]-elimination[26] to give the desired product **25** though in low yield (28%).

The loss of material by the competing [1,6]-elimination (giving **23**) could be avoided by using malodinitril. This one pot syntheses (Scheme 9) provided the racemic products **28a–c** in 69, 69, and 71% yield presumably by [1,2,(3)5′]-elimination[26] of the intermediates **27**. The orientation selectivity in the reactions of **22** and **26** with **1** is remarkable: the less basic though sterically easier primary amino group undergoes the Michael addition.

The chemical structures of the racemic compounds **25** and **28** are confirmed by the analytical and spectroscopic data. The formation of the imidazolidine ring with elimination of the amine in the last reaction step is derived from the molecular ion peak in the mass spectra, the 5-ring-CO vibrations above 1750 cm^{-1} in the IR spectra and the ^2J coupling constants of the methylene protons (**25**: 18.1 Hz; **28a**: 16.1 Hz; **28b**: 16.5 Hz; **28c**: 16.5 Hz) in the ^1H NMR spectra. No *cis*/*trans*-stereoisomers can be distinguished in **25** and **28** as the 4-N is almost planar. According to B3LYP/6-31G* density function calculations the 3,4,8,9-dihedrals of the two conformers of **28c** that differ in their energy content by 0.10 kcal mol^{-1} assume the values of 0.33° and −0.61° very close to zero.



a: R = H, R′ = C_2H_5, Ar = C_6H_5
b: R = R′ = CH_3, Ar = 4-$CH_3C_6H_4$
c: R = H, R′ = CH_3, Ar = 2-ClC_6H_4

Scheme 9. One-pot synthesis of cyano-imidazo[1,2-*c*]pyrimidines from benzaldehyde, malodinitril, and thiourea.

Imidazo[1,2-*c*]pyrimidines are important heterocycles in the field of antimicrobial agents.[47] This adds practical value to our versatile synthetic scheme. Previously, imidazo[1,2-*c*]pyrimidines were prepared by condensation of 4-amino-pyrimidines with α-halogenocarbonyls,[47–49] reaction of 4-halogenopyrimidines with aminoacetaldehyde diethyl-acetal,[49,50] cyclization of 4-halogenopyrimidines with 4-(2-chloroethyl)-amino compounds,[51] twofold ring closure of 1-methylthio-2-azabuta-1,3-diene-4,4-dicarbonitrile with ethylenediamine,[52] the treatment of *N*-acyl imidates with imidazolidine ketene aminals under microwave irradiation,[53] and the reaction of cytidine with β-acetyl-vinyl-triphenylphosphonium bromide.[54] Much waste is produced in all of these rather laborious inefficient reaction sequences. The present one pot technique has the advantage of starting with easily accessible and neutral starting materials while minimizing the amount of wastes.

3. Conclusion

Versatile thioureidoacetamides (**1a**–**h**) are environmentally benign building blocks. They were successfully used in various syntheses of heterocyclic compounds in good and even quantitative yields in one-pot reaction cascades. We describe here the benign synthesis and characterization of 28 compounds out of **1** with 12 different reagents; 21 of them are new compounds with potential biological activities. It proved particularly favorable to use in several cases solid-state or neat stoichiometric conditions instead of solution reactions. The structures of all compounds were carefully elucidated by spectroscopic, chemical and computational means. In some cases intermediates could be spectroscopically detected if our milder reaction conditions were chosen. Many of the new compounds may be useful for pharmacological testing. This feature appears interesting as the starting materials can be synthesized without wastes and the products described here are also formed waste-less (**4/5**) or with minimum waste (higher yields) at a very high atom economy.

4. Experimental

4.1. General methods

Melting points were determined with a Gallenkamp melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded with a Perkin–Elmer 1720-X FT-IR spectrometer using potassium bromide pellets. All NMR spectra were taken at a Bruker WP 300 at 300 MHz (^{1}H) or 75 MHz (^{13}C). $CDCl_3$/DMSO-d_6 mixtures contained up to 25% DMSO-d_6. ^{13}C peak assignments were based on spectra simulations in the Specinfo database. Mass spectra were obtained on a Finnigan MAT 212 System. The ball-mill was a Retsch MM 2000 with a 10 mL stainless steel beaker and balls. B3LYP (basis set 6-31G*) calculations with full geometry optimization were performed with the program TITAN, version 1.01 of Wavefunction, Inc., Irvine, USA.

4.2. General procedure for the reaction of thioureido-acetamides 1 with phenacyl bromide (2)

2.00 mmol of the solid thioureido-acetamide (**1a**–**c**) and 398 mg (2.00 mmol) of solid phenacyl bromide (**2**) were ball-milled at room temperature for 30 min. After drying at 0.01 bar at 80°C quantitative yields of the pure hydrobromides **4** were obtained in all cases. The salts were washed with 5% Na_2CO_3 solution to afford the free bases **5** in pure form.

4.2.1. *N*,*N*-Dimethyl-2-(4-phenyl-thiazole-2-yl-amino)-acetamide hydrobromide (4a). Yield 684 mg (100%); mp 238–240°C (dec.); IR (KBr) cm^{-1} 3254 (NH), 1647 (CO); ^{1}H NMR (D_2O) δ 2.81 (s, 3H), 2.96 (s, 3H), 4.35 (s, 2H), 7.44 (m, 3H), 7.56 (m, 3H).

4.2.2. *N*,*N*-Dimethyl-2-(4-phenyl-thiazole-2-yl-amino)-acetamide (5a). Yield 514 mg (98%); mp 185–186°C; IR (KBr) cm^{-1} 3443, 3282 (NH), 1654 (CO); ^{1}H NMR ($CDCl_3$/DMSO-d_6) δ 3.10 (s, 6H), 4.25 (d, J=4 Hz, 2H), 6.76 (s, 1H), 6.82 (bp, 1NH), 7.26 (ψt, 1H), 7.33 (ψt, 2H), 7.83 (ψd, 2H); ^{13}C NMR ($CDCl_3$/DMSO-d_6) δ 34.51, 34.98, 44.81, 100.19, 124.86 (2C), 126.34, 127.37 (2C), 139.98, 149.68, 166.75 (C=N), 167.18 (C=O); HRMS (CI, *i*-C_4H_{10}) *m*/*z* found 262.0894 calcd for $C_{13}H_{16}N_3OS$ 262.0910 $(M+H)^+$.

4.2.3. *rac*-*N*-Methyl-2-(4-phenyl-thiazole-2-yl-amino)-propionamide hydrobromide (4b). Yield 684 mg (100%); mp 195–196°C; IR (KBr) cm^{-1} 3316, 3227 (NH), 1680 (CO); ^{1}H NMR (D_2O) δ 1.58 (d, J=7 Hz, 3H), 2.72 (s, 3H), 4.21 (q, J=7 Hz, 1H), 7.50 (m, 5H).

4.2.4. *rac*-*N*-Methyl-2-(4-phenyl-thiazole-2-yl-amino)-propionamide (5b). Yield 516 mg (99%); mp 112°C; IR (KBr) cm^{-1} 3411, 3359, 3295, 3212 (NH), 1648 (CO); ^{1}H NMR ($CDCl_3$) δ 1.52 (d, J=7 Hz, 3H), 2.81 (d, J=4 Hz, 3H), 4.31 (quin, J=7 Hz, 1H), 5.88 (bd, J=7 Hz, 1NH), 6.65 (bp, 1NH), 6.73 (s, 1H), 7.25–7.42 (m, 3H), 7.78 (ψd, 2H); ^{13}C NMR ($CDCl_3$) δ 18.56, 26.25, 55.16, 101.95, 125.97 (2C), 127.79, 128.58 (2C), 134.66, 151.27, 167.86 (C=N), 173.24 (C=O); HRMS (CI, *i*-C_4H_{10}) *m*/*z* found 262.0898 calcd for $C_{13}H_{16}N_3OS$ 262.0910 $(M+H)^+$.

4.2.5. 2-(*N*-Methyl-acetamidyl-2-amino)-3,4-diphenyl-thiazolium bromide (4c). Yield 808 mg (100%); mp 194–195°C; IR (KBr) cm^{-1} 3259 (NH), 1682 (CO); ^{1}H NMR ($CDCl_3$) δ 2.81 (d, J=4 Hz, 3H), 5.40 (s, 2H), 6.53 (s, 1H), 7.55 (m, 10H), 8.0 (bq, J=4 Hz, 1NH).

4.2.6. 2-(*N*-Methyl-acetamidyl-2-imino)-3,4-diphenyl-thiazoline (5c). Yield 633 mg (98%); mp 194–195°C; IR (KBr) cm^{-1} 3408, 3319 (NH), 1660 (CO); ^{1}H NMR ($CDCl_3$) δ 1.61 (s, 1H, NH), 2.86 (d, J=4 Hz, 3H), 4.35 (s, 2H), 5.88 (s, 1H), 7.17 (m, 3H), 7.31–7.40 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 26.19, 50.43, 96.29, 121.49 (2C), 123.55, 128.92 (2C), 129.02 (2C), 129.54 (2C), 130.55, 140.70, 150.28, 160.94 (C=N), 169.01 (C=O); HRMS (CI, *i*-C_4H_{10}) *m*/*z* found 324.1171 calcd for $C_{18}H_{18}N_3OS$ 324.1171 $(M+H)^+$.

4.3. General procedure for the reaction of thioureido-acetamides 1 with oxalyl dichloride (6)

A solution of 5.0 mmol of the thioureido-acetamide (**1a**, **f**,

g) in 10 mL of dry tetrahydrofurane was cooled to −10°C and 0.70 g (5.0 mmol) of **6** in 5 mL of dry THF was slowly added through a dropping funnel. Thereafter the solution was stirred over a period of 30 min at room temperature and for further 30 min under reflux. The pure product that crystallized upon cooling was collected by filtration, washed with 5 mL of THF and dried in a vacuum.

4.3.1. 2-(4,5-Dioxo-2-thioxo-imidazolidine-1-yl)-*N*,*N*-dimethylacetamide (9a). Yield 914 mg (85%); mp 265°C (dec.); IR (KBr) cm^{-1} 1783, 1647 (CO); ^1H NMR (DMSO-d_6) δ 2.81 (s, 3H), 3.06 (s, 3H), 4.68 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 35.19, 35.75, 41.90, 155.75 (C-4), 157.31 (C-5), 164.06 (C═O), 182.47 (C═S); HRMS (EI, 70 eV) *m/z* found 215.0316 calcd for $C_7H_9N_3O_3S$ 215.0321 (M^+).

4.3.2. 2-(3-Phenyl-4,5-dioxo-2-thioxo-imidazolidine-1-yl)-*N*,*N*-dimethylacetamide (9f). Yield 1.15 g (79%); mp 180–181°C; IR (KBr) cm^{-1} 1784, 1660 (CO); ^1H NMR ($CDCl_3$) δ 3.01 (s, 3H), 3.14 (s, 3H), 4.85 (s, 2H), 7.38 (m, 2H), 7.52 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 35.97, 36.29, 42.90, 127.99 (2C), 129.37 (2C), 129.83, 154.61 (C-4), 158.88 (C-5), 163.67 (C═O), 180.21 (C═S); HRMS (EI, 70 eV) *m/z* found 291.0680 calcd for $C_{13}H_{13}N_3O_3S$ 291.0680 (M^+).

4.3.3. 2-(3-Ethyl-4,5-dioxo-2-thioxo-imidazolidine-1-yl)-*N*,*N*-dimethylacetamide (9g). Yield 945 mg (76%); mp 179°C; IR (KBr) cm^{-1} 1777, 1661 (CO); ^1H NMR ($CDCl_3$/DMSO-d_6) δ 1.21 (t, *J*=7 Hz, 3H), 2.97 (s, 3H), 3.08 (s, 3H), 3.81 (q, *J*=7 Hz, 2H), 4.78 (s, 2H); ^{13}C NMR ($CDCl_3$/DMSO-d_6) δ 12.85, 36.37, 37.38, 42.53, 48.42, 154.61 (C-4), 158.81 (C-5), 171.39 (C═O), 183.62 (C═S); HRMS (CI, *i*-C_4H_{10}) *m/z* found 244.0724 calcd for $C_9H_{14}N_3O_3S$ 244.0678 $(M+H)^+$.

4.4. Spectroscopic detection of intermediates 8

4.4.1. 2-(*N*,*N*-Dimethylacetamidylamino)-4,5-dioxothiazoline (8′a). 322 mg (2.00 mmol) **1a** and 254 mg (2.00 mmol) **6** were mixed at −10°C. After 30 min rest stirring was started for 30 min at −20°C and NMR spectra of the reaction mixture were measured. Recrystallization from ethanol gave 318 mg (74%) **9a**. ^1H NMR ($CDCl_3$/DMSO-d_6) peaks attributed to **8′a** (82% by integration): δ 2.69 (s, 3H), 2.82 (s, 3H), 4.19 (s, 2H); ^{13}C NMR ($CDCl_3$/DMSO-d_6) peaks attributed to **8′a**: δ 34.21, 35.27, 35.63, 153.15, 157.76, 159.98, 163.70. The minor peaks were assigned to thiohydantoin (9%) and three further products (9%) but not **9a**.

4.4.2. 2-(*N*,*N*-Dimethylacetamidylimino)-4,5-dioxo-3-phenyl-thiazolidine (8f). 254 mg (2.00 mmol) **6** were solidified in a 10 mL ball-mill beaker at −30°C. 474 mg (2.00 mmol) precooled crystals of **1f** were added and milling was started at 50 Hz for 30 min at −30°C. The solid mixture was analyzed by NMR spectroscopy. Its composition was 31% **8f** (or **8″f**), 61% **9f**, 6% unreacted **1f** and 2% thiohydantoin. ^1H NMR ($CDCl_3$/DMSO-d_6) peaks attributed to **8f** (or **8″f**): 3.02 (s, 3H), 3.11 (s, 3H), 4.88 (s, 2H), 6.95 (ψd, 2H), 7.21 (ψt, 1H), 7.34 (m, 2H). After recrystallization of the mixture from ethanol a 83% yield of **9f** (483 mg) was collected by filtration.

4.5. General procedure for the reaction of thioureidoacetamides 1 with benzils 10

A solution of 10 mmol of **1**, 10 mmol of **10** and 200 mg of NaOH in 10 mL of ethanol, containing 1 mL of water, was heated at reflux. After 15 h water was added to the cooled reaction mixture and the precipitated product **14** was filtered off and recrystallized from ethanol.

4.5.1. 2-(5,5-Diphenyl-thiohydantoin-3-yl)-*N*,*N*-dimethylacetamide (14a). Yield 1.87 g (53%); mp 229°C; IR (KBr) cm^{-1} 3430 (NH), 1743, 1660 (CO); ^1H NMR ($CDCl_3$/DMSO-d_6) δ 2.64 (bp, 1NH), 3.0 (s, 3H), 3.11 (s, 3H), 4.68 (s, 2H), 7.34 (m, 6H), 7.45 (m, 4H); ^{13}C NMR ($CDCl_3$/DMSO-d_6) δ 35.44, 35.98, 41.72, 71.99, 127.13 (4C), 128.01 (2C), 128.15 (4C), 137.95 (2C), 164.65 (C-4), 173.96 (C═O), 181.16 (C═S); MS (EI, 70 eV) *m/z* (%): 353 (100), 309 (14), 280 (35), 224 (14), 194 (13), 180 (Ph_2CN^+, 10), 165 (28); HRMS (CI, *i*-C_4H_{10}) *m/z* found 354.1276 calcd for $C_{19}H_{20}N_3O_2S$ 354.1276 $(M+H)^+$.

4.5.2. *rac*-2-(5,5-Diphenyl-thiohydantoin-3-yl)-*N*-methylpropionamide (14b). Yield 1.73 g (49%); mp 257–258°C; IR (KBr) cm^{-1} 3407 (NH), 1749, 1676 (CO); ^1H NMR ($CDCl_3$/DMSO-d_6) δ 1.64 (d, *J*=7 Hz, 3H), 2.73 (d, *J*=4 Hz, 3H), 2.86 (s, 1NH), 5.35 (q, *J*=7 Hz, 1H), 6.91 (bq, *J*=4 Hz, 1NH), 7.36 (m, 10H); ^{13}C NMR ($CDCl_3$/DMSO-d_6) δ 13.66, 25.73, 51.64, 70.58, 126.30 (2C), 126.90 (2C), 127.70 (2C), 127.89 (4C), 137.49, 138.10, 168.48 (C-4), 173.01 (C═O), 181.13 (C═S); MS (EI, 70 eV) *m/z* (%): 353 (38), 322 (96), 294 (95), 225 (33), 194 (38), 182 (72), 180 (Ph_2CN^+, 29), 165 (100); HRMS (CI, *i*-C_4H_{10}) *m/z* found 354.1278 calcd for $C_{19}H_{20}N_3O_2S$ 354.1278 $(M+H)^+$.

4.5.3. 2-(5,5-Di-(4-methoxyphenyl)-thiohydantoin-3-yl)-*N*,*N*-dimethylacetamide (14c). Yield 1.86 g (45%); mp 112–115°C (dec.); IR (KBr) cm^{-1} 3405 (NH), 1744, 1661 (CO); ^1H NMR ($CDCl_3$/DMSO-d_6) δ 2.80 (bp, 1NH), 2.98 (s, 3H), 3.10 (s, 3H), 3.79 (s, 6H), 4.61 (s, 2H), 6.88 (ψd, 4H), 7.38 (ψd, 4H); ^{13}C NMR ($CDCl_3$/DMSO-d_6) δ 35.28, 35.75, 41.49, 54.72 (2C), 71.05, 113.31 (2C), 128.24 (2C), 130.04 (2C), 158.97 (2C), 164.57 (C-4), 174.28 (C═O), 180.75 (C═S); MS (EI, 70 eV) *m/z* (%): 423 (100), 369 (8), 340 (24), 284 (25), 254 (63), 242 (29), 240 (Ar_2CN^+, 18), 226 (28), 211 (18); HRMS (CI, *i*-C_4H_{10}) *m/z* found 414.1528 calcd for $C_{21}H_{24}N_3O_4S$ 414.1534 $(M+H)^+$.

4.6. General procedure for the reaction of thioureidoacetamides 1 with dimethyl acetylene dicarboxylate (15)

(a) In solution. A solution of 10 mmol of **1** and 10 mmol of **15** in 100 mL ethanol was refluxed for 2 h. After cooling pure **17** crystallized in the cases **b** and **e** and mixtures of **17** and **18** in the cases **d** and **h**. The crude reaction mixtures were analyzed by NMR spectroscopy as **17** and **18**. These were separated by recrystallization from ethyl acetate: **18d/18h** were soluble in hot ethyl acetate and **17d/17h** remained insoluble. The latter were recrystallized from DMSO.

(b) Neat. 2.00 mmol of **1** and 2.00 mmol of **15** were weighed into a 10 mL ball-mill vessel. The mixture became

immediately solid and was ball-milled at 25 Hz for 1 h. The crude reaction mixture was analyzed by NMR spectroscopy. Workup was done as described in (a).

4.6.1. *rac*-(5-(*Z*)-Methoxycarbonylmethylene)-2-(*N*-methyl-2-propionamidyl-2-imino)-thiazolidine-4-one (17b). (a) Yield 2.33 g (86%); mp 248°C (dec., ethanol); IR (KBr) cm^{-1} 3301, 2980, 1701, 1660, 1598, 1534; ^1H NMR (DMSO-d_6) δ 1.36 (d, J=7 Hz, 3H), 2.61 (d, J=4 Hz, 3H), 3.79 (s, 3H), 4.66 (q, J=7 Hz, 1H), 6.64 (s, 1H), 8.12 (bp, 1NH); ^{13}C NMR (DMSO-d_6) δ 18.35, 25.57, 52.43, 53.86, 114.76, 147.72 (C-5), 166.30 (C═O), 170.62 (C═N), 174.82 (C═O), 177.75 (C═O); MS (EI, 70 eV): *m/z* (%) 271 (M^+ 23), 204 (17), 213 (100), 182 (16), 154 (22), 117 (30); HRMS (CI, *i*-C_4H_{10}) *m/z* found 272.0705 calcd for $C_{10}H_{14}N_3O_4S$ 272.0711 $(M+H)^+$. (b) Yield 76% after recrystallization from ethyl acetate.

4.6.2. 5-[(*Z*)-Methoxycarbonylmethylene]-2-(*N*-methyl-2-acetamidyl-2-imino)-thiazolidine-4-one (17d). (a) The product ratio **17d/18d** was 0.43:1.0; after extraction by refluxing with 25 mL of hot ethyl acetate for 10 min, hot filtration and recrystallization of the residue from DMSO 0.41 g (16%) **17d**, mp 270°C (dec., DMSO) was obtained; IR (KBr) cm^{-1} 3286, 3221, 1708, 1685, 1669, 1635, 1581; ^1H NMR (DMSO-d_6) δ 2.60 (d, J=4 Hz, 3H), 3.78 (s, 3H), 4.19 (s, 2H), 6.63 (s, 1H), 8.04 (bp, 1NH), 10.21 (bp, 1NH); ^{13}C NMR (DMSO-d_6) δ 25.49, 47.0, 52.45, 114.80, 147.79 (C-5), 166.28 (C═O), 167.03 (C═N), 175.90 (C═O), 177.63 (C═O); MS (EI, 70 eV): *m/z* (%) 257 (M^+, 41), 226 (16), 201 (46), 200 (98), 199 (100), 172 (17), 168 (29), 144 (16); HRMS (CI, *i*-C_4H_{10}) *m/z* found 258.0435 calcd for $C_9H_{12}N_3O_4S$ 258.0441 $(M+H)^+$. (b) The product ratio **17d/18d** was 2.0:1.0; 54% **17d** after recrystallization.

4.6.3. 2-Imino-5-[(*Z*)-methoxycarbonylmethylene]-3-(*N*-methyl-2-acetamidyl)-thiazolidine-4-one (18d). (a) The extract from **17d** was evaporated to dryness and recrystallized from ethanol; yield 1.52 g (59%); mp 210°C; IR (KBr) cm^{-1} 3281, 1725, 1683, 1658, 1635, 1609; ^1H NMR ($CDCl_3$/DMSO-d_6) δ 2.64 (d, J=4 Hz, 3H), 3.80 (s, 3H), 4.31 (s, 2H), 6.72 (s, 1H), 8.0 (bp, 1NH), 9.97 (bp, 1NH); ^{13}C NMR ($CDCl_3$/DMSO-d_6) δ 23.74, 41.73, 50.48, 111.74, 141.56 (C-5), 151.80 (C═N), 162.44 (C═O), 163.89 (C═O), 163.96 (C═O); MS (EI, 70 eV) *m/z* (%): 257 (M^+, 4), 226 (6), 202 (8), 201 (10), 200 (100), 187 (4), 172 (10), 141 (10); HRMS (EI, 70 eV) *m/z* found 257.0469 calcd for $C_9H_{11}N_3O_4S$ 257.0468 (M^+). (b) Yield: 26% after extraction and recrystallization.

4.6.4. *rac*-5-[(*Z*)-Methoxycarbonylmethylene]-2-(*N*-methyl-2-*i*-butyl-acetamidyl-2-imino)-thiazolidine-4-one (17e). Yield 2.60 g (83%); mp 210°C (ethanol); IR (KBr) cm^{-1} 3319, 1700, 1657, 1588, 1531; ^1H NMR (DMSO-d_6) δ 0.84 (m, 6H), 1.55 (m, 4H), 2.60 (d, J=4 Hz, 3H), 3.76 (s, 3H), 4.63 (t, J=7 Hz, 1H), 6.62 (s, 1H), 8.26 (q, J=4 Hz, 1NH); ^{13}C NMR (DMSO-d_6) δ 21.6, 22.7, 24.4, 25.5, 41.1, 52.4, 56.9, 114.7, 147.6 (C-5), 166.3 (C═O), 170.3 (C═N), 175.1 (C═O), 177.7 (C═O); MS (EI, 70 eV) *m/z* (%): 313 (M^+, 8), 282 (4), 257 (48), 255 (100), 213 (78), 199 (44), 151 (8); HRMS (EI, 70 eV) *m/z* found 313.1097 calcd for $C_{13}H_{19}N_3O_4S$ 313.1097 (M^+).

4.6.5. 2-(*N*-Ethyl-2-acetamidyl-2-imino)-5-[(*Z*)-methoxycarbonylmethylene]-thiazolidine-4-one (17h). (a) The product ratio **17h/18h** was 0.59:1.0; after extraction by refluxing with 25 mL of hot ethyl acetate for 10 min, hot filtration and recrystallization of the residue from DMSO 0.52 g (19%) **17h** was obtained; mp 250–251°C (dec.); IR (KBr) cm^{-1} 3299, 3219, 1708, 1687, 1664, 1585; ^1H NMR (DMSO-d_6) δ 1.02 (t, J=7 Hz, 3H), 3.10 (m, 2H), 3.76 (s, 3H), 4.16 (s, 2H), 6.61 (s, 1H), 8.10 (bp, 1 NH), 10.13 (bp, 1 NH); ^{13}C NMR (DMSO-d_6) δ 14.54, 33.55, 47.03, 52.45, 114.80, 147.82 (C-5), 166.29 (C═O), 166.29 (C═N), 175.89 (C═O), 177.65 (C═O); MS (EI, 70 eV) *m/z* (%) 271 (M^+ 8), 240 (6), 200 (98), 199 (100), 168 (27), 144 (7);188 (42), 172 (47), 141 (56); HRMS (CI, *i*-C_4H_{10}) *m/z* found 272.0705 calcd for $C_{10}H_{14}N_3O_4S$ 272.0699 $(M+H)^+$. (b) The product ratio **17h/18h** was 1.5:1.0; 1.36 g (50%) **17h** after extraction and recrystallization of the residue.

4.6.6. 2-Imino-3-(*N*-ethyl-2-acetamidyl)-5-[(*Z*)-methoxycarbonylmethylene]-thiazolidine-4-one (18h). (a) The extract from **17h** was evaporated to dryness and recrystallized from ethanol; yield 1.45 g (54%); mp 226–227°C (dec.); IR (KBr) cm^{-1} 3294, 1723, 1687, 1662, 1640; ^1H NMR ($CDCl_3$/DMSO-d_6) δ 1.06 (t, J=7 Hz, 3H), 3.14 (m, 2H), 3.81 (s, 3H), 4.38 (s, 2H), 6.73 (s, 1H), 8.02 (bp, 1NH), 9.90 (bp, 1NH); ^{13}C NMR ($CDCl_3$/DMSO-d_6) δ 12.83, 32.03, 41.83, 50.54, 111.91, 141.61 (C-5), 152.01 (C═N), 162.56 (C═O), 163.23 (C═O), 164.06 (C═O); MS (EI, 70 eV) *m/z* (%) 271 (M^+ 8), 240 (6), 200 (98), 199 (100), 168 (27), 144 (7),188 (42), 172 (47), 141 (56); HRMS (CI, *i*-C_4H_{10}) *m/z* found 272.0705 calcd for $C_{10}H_{14}N_3O_4S$ 272.0699. (b) Yield 33% after extraction and recrystallization.

4.6.7. 4-[(*Z*)-Methoxycarbonylmethylene]-1-(*N*-methyl-2-acetamidyl)-2-thioxo-imidazolidine-5-one (21a). 783 mg (8.90 mmol) of glycine *N*-methylamide (**20**) and 1.79 g (8.90 mmol) of the thiocyanato ester **19** in 50 mL *i*-propanol were stirred at room temperature and after 3 h the mixture was refluxed for 15 min. After cooling, the precipitate was filtered and recrystallized from ethanol. Yield 824 mg (36%); mp 235°C (dec.); IR (KBr) cm^{-1} 3292, 1762, 1681, 1662; ^1H NMR ($CDCl_3$/DMSO-d_6) δ 2.72 (d, J=4 Hz, 3H), 3.84 (s, 3H), 4.50 (s, 2H), 5.81 (s, 1H), 7.71 (s, 1NH), 7.86 (bp, 1NH); ^{13}C NMR (DMSO-d_6) δ 25.47, 43.04, 51.82, 96.33, 137.32, 163.25 (C-4), 164.59 (C═O), 165.29 (C═O), 180.05 (C═S); HRMS (CI, *i*-C_4H_{10}) *m/z* found 258.0450 calcd for $C_9H_{12}N_3O_4S$ 258.0445 $(M+H)^+$.

4.7. One pot synthesis of 23 and 25

1.13 g (10.0 mmol) ethyl cyanoacetate, 1.06 g (10.0 mmol) freshly distilled benzaldehyde, 1.47 g (10.0 mmol) *N*-methyl-2-thioureido acetamide (**1d**) and 1.38 g K_2CO_3 in 100 mL dry ethanol were heated at reflux. After 5 h the reaction mixture was cooled and evaporated to dryness. The solid residue was treated with 100 mL of hot water and acidified with acetic acid. The immediately obtained precipitate of **25** was collected by filtration. **23** crystallized from the filtrate after standing overnight. Both products were purified by recrystallization from ethanol.

4.7.1. 5-Cyano-3-(*N*-methyl-2-acetamidyl)-6-phenyl-2-thiouracil (23). Yield 0.63 g (21%); mp 230°C (dec., ethanol); IR (KBr) cm^{-1} 3280, 2218, 1682, 1650, 1607, 1534; ^1H NMR ($CDCl_3$/DMSO-d_6) δ 2.72 (s, 3H), 5.02 (s, 2H), 7.63 (m, 5H), 7.83 (s, 1NH); HRMS (CI, *i*-C_4H_{10}) *m/z* found 301.0754 calcd for $C_{14}H_{13}N_4O_2S$ 301.0753 $(M+H)^+$.

4.7.2. *rac*-8-Ethoxycarbonyl-2-oxo-7-phenyl-5-thioxo-1,2,3,5,6,7-hexahydro-imidazo[1,2-*c*]pyrimidine (25). Yield 0.90 g (28%); mp 226°C (ethanol); IR (KBr) cm^{-1} 3159, 1754, 1701, 1679; ^1H NMR ($CDCl_3$/DMSO-d_6) δ 1.17 (t, J=7 Hz, 3H), 4.14 (q, J=7 Hz, 2H), 4.32 (AB, J=18 Hz, 1H), 4.66 (BA, J=18 Hz, 1H), 5.37 (d, J=3 Hz, 1H), 7.33 (m, 5H), 9.84 (bp, 1NH), 10.49 (bs, 1NH); ^{13}C NMR ($CDCl_3$/DMSO-d_6) δ 13.19, 49.24 (C-3), 53.17 (C-6), 59.03, 81.21 (C-8), 125.60 (2C), 125.80, 127.41 (2C), 141.98 (q arom.-C), 143.82 (C-9), 163.72 (C═O), 167.33 (C═O), 172.18 (C═S); HRMS (CI, *i*-C_4H_{10}) *m/z* found 318.0878 calcd for $C_{15}H_{16}N_3O_3S$ 318.0875 $(M+H)^+$.

4.8. General procedure for the synthesis of imidazo[1,2-*c*]pyrimidines (28)

10 mmol of the freshly distilled aldehyde, 10 mmol (660 mg) of malodinitrile, 1.38 g of K_2CO_3 and 10 mmol of **1** were heated to reflux in 20 mL of dry ethanol for 4 h. After cooling the solution was acidified with 50% aqueous acetic acid. The precipitate was recrystallized from ethanol. The resulting ethanol complexes were freed from the solvent by heating in a vacuum at 80°C.

4.8.1. 8-Cyano-2-oxo-7-phenyl-5-thioxo-1,2,3,5,6,7-hexahydro-imidazo[1,2-*c*]pyrimidine (28a). Yield 1.92 g (71%); mp 218°C (dec., ethanol); IR (KBr) cm^{-1} 3431, 3200, 2199, 1784, 1754, 1683; ^1H NMR ($CDCl_3$/DMSO-d_6) δ 4.09 (AB, J=19 Hz, 1H), 4.30 (BA, J=19 Hz, 1H), 4.86 (s, 1H), 7.08 (m, 5H), 9.41 (bs, 1NH), 12.20 (bs, 1NH); ^{13}C NMR ($CDCl_3$/DMSO-d_6) δ 50.34 (C-7), 54.48 (C-3), 61.75 (C-8), 115.27 (C≡N), 125.81 (2C), 127.96, 128.24 (2C), 140.43 (q arom. C), 145.80 (C-9), 167.78 (C═O), 172.20 (C═S); HRMS (CI, *i*-C_4H_{10}) *m/z* found 271.0661 calcd for $C_{13}H_{11}N_4OS$ 271.0660 $(M+H)^+$.

4.8.2. 8-Cyano-2-oxo-7-(*p*-tolyl)-5-thioxo-1,2,3,5,6,7-hexahydro-imidazo[1,2-*c*]pyrimidine (28b). Yield 1.97 g (69%); mp: 240°C (dec., ethanol); IR (KBr) cm^{-1} 3348, 3133, 2211, 1781, 1754, 1689; ^1H NMR ($CDCl_3$/DMSO-d_6) δ 2.34 (s, 3H), 4.40 (AB, J=16.5 Hz, 1H), 4.58 (BA, J=16.5 Hz, 1H), 5.14 (s, 1H), 7.21 (m, 4H), 9.78 (bs, 1NH), 12.18 (bs, 1NH); ^{13}C NMR ($CDCl_3$/DMSO-d_6) δ 20.66, 50.64 (C-7), 54.64 (C-3), 62.37 (C-8), 115.56 (C≡N), 126.03 (2C), 129.18 (2C), 129.53, 138.14 (q arom.-C), 145.92 (C-9), 168.06 (C═O), 172.50 (C═S); HRMS (CI, *i*-C_4H_{10}) *m/z* found 285.1042 calcd for $C_{14}H_{13}N_4OS$ 285.1037 $(M+H)^+$.

4.8.3. 8-Cyano-2-oxo-7-(2-chlorophenyl)-5-thioxo-1,2,3,5,6,7-hexahydro-imidazo[1,2-*c*]pyrimidine (28c). Yield 1.99 g (69%); mp 262°C (dec., ethanol); IR (KBr) cm^{-1} 3500, 3165, 3034, 2977, 2206, 1780, 1752, 1702; ^1H NMR ($CDCl_3$/DMSO-d_6) δ 4.45 (AB, J=16 Hz, 1H), 4.57 (BA, J=16 Hz, 1H), 5.69 (s, 1H), 7.3–7.55 (m, 4H), 9.78 (bs, 1NH), 12.25 (bs, 1NH); ^{13}C NMR ($CDCl_3$/DMSO-d_6) δ 49.82 (C-7), 55.73 (C-3), 59.81 (C-8), 114.41 (C≡N), 126.66, 128.50, 128.77, 128.92, 130.92, 137.20 (q arom. C), 145.80 (C-9), 167.44 (C═O), 171.58 (C═S); HRMS (CI, *i*-C_4H_{10}) *m/z* found 305.0264 calcd for $C_{13}H_9ClN_4OS$ 305.0264 (M^+).

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