Pergamon

Tetrahedron 57 (2001) 2031–2038

TETRAHEDRON

Synthesis of functionalised pyrazolones and imidazolines/imidazoles through divergent cyclisation reactions

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Received 15 September 2000; revised 27 November 2000; accepted 21 December 2000

Abstract—The base-promoted reactions of easily accessible α-aminohydrazones represent a simple and efficient method for the preparation of both 1-substituted and 1-unsubstituted-4-aminocarbonyl-1*H*-pyrazol-5(2*H*)-ones, whereas the copper promoted reactions provide a divergent facile regiocontrolled synthesis of the imidazoline/imidazole ring system. The copper-promoted reaction of the α-benzylamino-hydrazone produces a 2-oxo-1,4-diazadiene derivative. Finally, the imidazolines can be easily hydrolyzed to α-ketohydrazones. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

The presence of the azo group in the heterodiene system of 1,2-diaza-1,3-butadienes favours nucleophilic attack to afford Michael type adducts. The 1,4-conjugate addition of Grignard reagents, anionic reagents, activated methylene and methine compounds and several oxygen, sulphur and nitrogen nucleophiles provides a route to hydrazone derivatives,[1] which are versatile building blocks for the construction of a variety of functionalised heterocycles through cyclisation processes.[2] In connection with our ongoing interest in developing new synthetic strategies for the construction of five-membered heterocyclic rings involving conjugated azoalkenes and transition metals,[3] we reported that the 1,4-addition of sarcosine or glycine ethyl ester on 1,2-diaza-1,3-butadienes leads to the corresponding α-aminohydrazone derivatives. These can undergo divergent base or copper(I) promoted annelation reactions to give functionalised pyrazolones or imidazolines/imidazoles, respectively.[4] The synthesis of functionalised pyrazolones and imidazoles is continuing to attract interest due to their pharmacological and reactivity properties. For example, the recent synthesis of a series of pyrazole derivatives has been reported to aid in the characterisation of the cannabinoid receptor binding sites, and also to serve as potentially useful therapeutic agents able to antagonise harmful side effects of cannabinoids.[5] Some alkynylpyrazoles show cholesterol synthesis-inhibiting activity.[6] Novel potent and selective tetrasubstituted imidazole inhibitors of p38MAP (mitogen-activated protein) kinase have activity in both cell-based assays of tumour necrosis factor α release and an animal model of rheumatoid arthritis.[7] So, with the aim of developing the title heterocyclic ring structures from α-aminohydrazones as precursors, we decided to assess the scope and limitations of this synthetic methodology.

2. Results and discussion

α-Aminohydrazones **3a**–**p**, readily obtained in good to excellent yields by the reaction between 4-alkoxycarbonyl-3-methyl-1,2-diaza-1,3-butadienes **1a**–**d** and amines **2a**–**e**,[8,9] can undergo base promoted heterocyclisation reactions at room temperature to produce the 1-aminocarbonyl-1*H*-pyrazol-5(2*H*)-ones **4a**–**e**. Smooth solvolytic cleavage of the group linked to the nitrogen atom in position 1 of **4a** led to the 1-unsubstituted-1*H*-pyrazol-5(2*H*)-one **5a** in 66% yield[10] (Scheme 1, Table 1).

This synthetic methodology can accomplish a new simple entry into 4-propargylamino-pyrazolones **4d,e**,[11] which may be of interest as potential cholesterol synthesis-inhibiting activity.

Furthermore, derivatives **3** can undergo a novel copper(I)-promoted reaction to give 1-ureido-2-imidazolines **6** (Scheme 2). The coordination of glycine and its derivatives to metal ions such as Cu(II), and Co(III) has been reported to

Keywords: α-aminohydrazones; pyrazolones; copper complexes; imidazolines/imidazoles.

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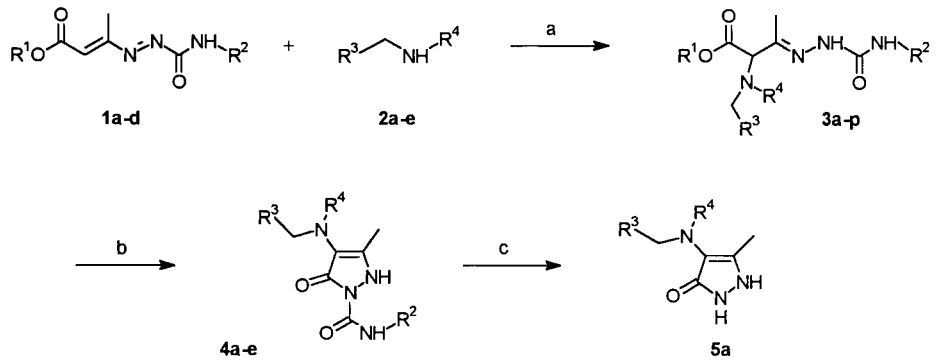
PII: S0040-4020(01)00022-9



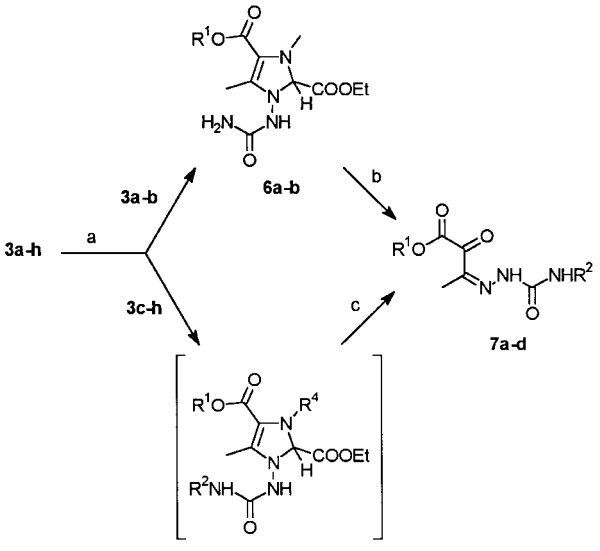
Scheme 1. *Reagents and conditions*: (a) MeOH/THF, room temperature ($NaOAc·3H_2O$ was added for **2a**, **2b** and **2d** which were purchased as hydrochloride salts); (b) EtOH/THF, NaH, room temperature: (c) EtOH, reflux.

Table 1. Compounds **3a**–**p**, **4a**–**e** and **5a**

Compound	R^1	R^2	R^3	R^4	Reaction time	Yield (%)
3a	Me	H	CO_2Et	Me	1 h	91
3b	Et	H	CO_2Et	Me	1 h	82
3c	Me	Ph	CO_2Et	Me	1 h	80
3d	Et	Ph	CO_2Et	Me	30 min	70
3e	Me	H	CO_2Et	H	4 h	88
3f	Et	H	CO_2Et	H	4 h	70
3g	Me	Ph	CO_2Et	H	3 h	90
3h	Et	Ph	CO_2Et	H	1 h	80
3i	Me	H	C≡CH	H	4 h	80
3j	Et	H	C≡CH	H	1 h	86
3k	Me	Ph	C≡CH	H	1 h	93
3l	Et	Ph	C≡CH	H	1 h	80
3m	Et	H	CN	H	3 h	66
3n	Me	Ph	CN	H	4 h	69
3o	Et	Ph	CN	H	4 h	70
3p	Me	H	Ph	H	3 h	72
4a	–	H	CO_2Et	Me	5 min	83 from **3a** 85 from **3b**
4b	–	Ph	CO_2Et	Me	5 min	93 from **3c** 89 from **3d**
4c	–	Ph	CO_2Et	H	5 min	81 from **3g** 85 from **3h**
4d	–	H	C≡CH	H	30 min	86 from **3i** 84 from **3j**
4e	–	Ph	C≡CH	H	30 min	98 from **3k** 86 from **3l**
5a	–	–	CO_2Et	Me	1 h	66

increase the reactivity of the α-methylene hydrogens.[12] The Kharasch–Sosnovsky reaction[13] represents a useful method for the functionalisation of C–H bonds and has been subject to substantial attention recently, as an expedient route to chiral allylic alcohols with the employment of amino acids as chiral ligands to copper.[14] The catalytic oxidation of α-carbon of ethers utilising binuclear copper(II) complex of 7-azaindole under oxygen atmosphere produced esters.[15] In recent years, binuclear complexes containing copper have received much attention in biochemistry.[16] These complexes play an important role in oxygen transport and oxidation in organisms.[17] Mechanistic study of the oxidative reactions and the kinetics and thermodynamics of copper(I)/dioxygen systems are of growing interest.[18] While the behaviour of these systems has been reported on related mimics for copper dependent monooxygenase,[19] there are few applications to organic synthesis.[20]

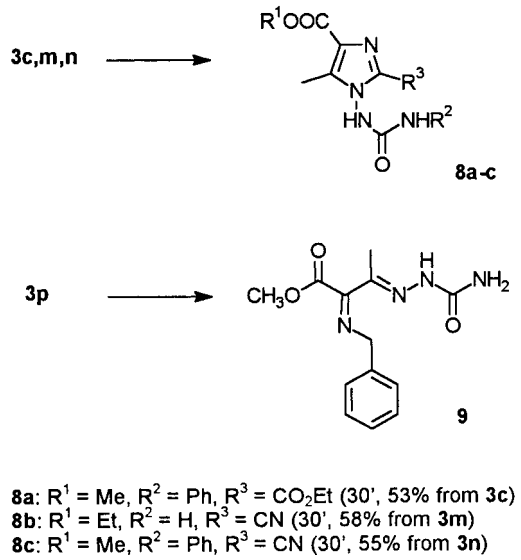
The α-aminohydrazones **3a**,**b** in the presence of a stoichiometric amount of copper(I) iodide gave, by precipitation, the 3,5-dimethyl-1-ureido-2,3-dihydro-1*H*-imidazole-2,4-dicarboxylates **6a**,**b** in THF, under oxygen atmosphere, in good yields (78% of **6a** and 83% of **6b**, Scheme 2). They were easily collected by filtration. The above reactions performed with a catalytic amount of copper(I) iodide resulted in the isolation of the same products in poor yields. With the α-aminohydrazones **3c**,**d** no precipitation occurred during the course of the reaction and usual work up of the crude mixture resulted in the isolation of the α-ketohydrazones **7c**,**d** in nearly quantitative yields. However, the ^1H NMR analysis of the crude product after evaporation of the tetrahydrofuran showed a signal pattern which can be attributed to the 2,3-dihydro-1*H*-imidazoles **6**. Moreover, when **6a**,**b** were reacted in $MeOH/H_2O$ **7a**,**b** were isolated in quantitative yields.[21,22] The ^1H NMR analysis of the crude product of the reaction of the α-aminohydrazones **3e**–**h** showed a more complex signal pattern and the corresponding α-ketohydrazones **7** were isolated in moderate yield (about 40%).



6a: R^1 = Me (78%)
6b: R^1 = Et (83%)

7a: R^1 = Me, R^2 = H (quant. from **6a**, 40% from **3e**)
7b: R^1 = Et, R^2 = H (quant. from **6b**, 42% from **3f**)
7c: R^1 = Me, R^2 = Ph (quant. from **3c**, 36% from **3g**)
7d: R^1 = Et, R^2 = Ph (quant. from **3d**, 36% from **3h**)

Scheme 2. *Reagents and conditions*: (a) THF, CuI, O_2, room temperature, 1 h; (b) MeOH, H_2O; (c) work up (water/EtOAc).



Scheme 3. *Reagents and conditions*: THF, CuBr, $Cu(OAc)_2$, $^tBuOOCOPh$, N_2, room temperature.

α-Ketohydrazones **7** were also obtained from the corresponding 1,2-hydrazino-hydrazones in the reaction with TFA in THF and MeOH and bubbling air.[22]

In order to achieve a better understanding of these latter results and widen the scope of this synthetic methodology, we performed the copper(I)-promoted reaction of α-aminohydrazones **3** in a stronger oxidising medium with the aim to favour the aromatisation of the corresponding 2,3-dihydro-1*H*-imidazole intermediate **6** to a more stable imidazole **8**. Both cyclisation and aromatisation reactions were carried out in one step starting from **3c**,**m**,**n** to give **8a**–**c** by a copper(I)-mediated peroxide process, widely used as an alternative method to oxidise a variety of dihydroheterocyclic compounds[23] (Scheme 3).

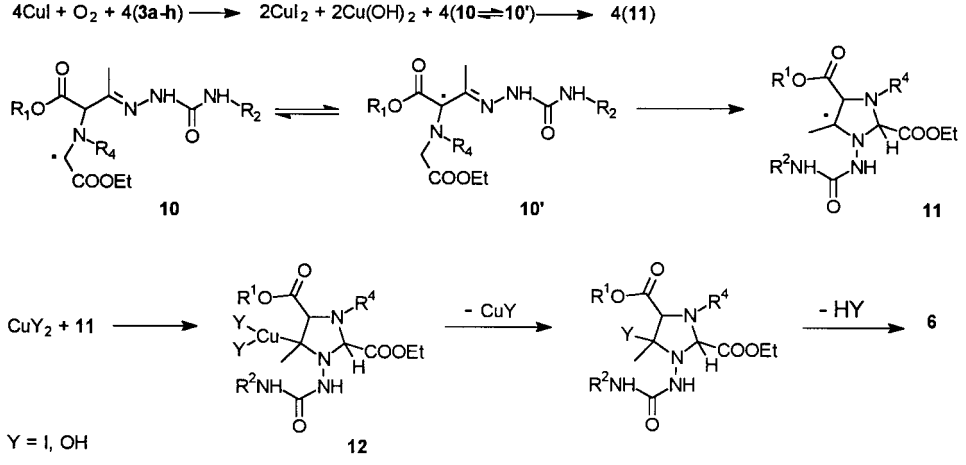
By contrast, the 3-aminocarbonylydrazono-2-benzyliminobutirric acid methyl ester **9** (40% yield) was isolated from the α-benzyl-aminohydrazone **3p** under the same reaction conditions, while the α-propargyl-aminohydrazones **3i**–**l** gave more complex reaction mixtures.

The proposed mechanism for the formation of the 2,3-dihydro-1*H*-imidazoles **6** is depicted in Scheme 4: (a) formation of (Cu^{III}–O^{-}⇔Cu^{II}–$O^{\cdot}$), as postulated in several works dealing with the oxidation of different compounds by the copper(I)/oxygen system;[24] (b) homolytic cleavage of CH bonds giving rise to stabilised radical intermediates **10** and **10′** arising from the selective cleavage by chelation of the α-hydrogen atoms of α-aminocarboxylic esters present in the molecule;[25] (c) formation of **11** via regioselective intramolecular attack on the carbon-nitrogen double bond; (d) generation of the σ-copper(III) complex **12** by oxidative addition of Cu(II) species; (e) reductive elimination regenerating copper(I) species; (f) β-elimination reaction providing the 2-imidazolines **6**.

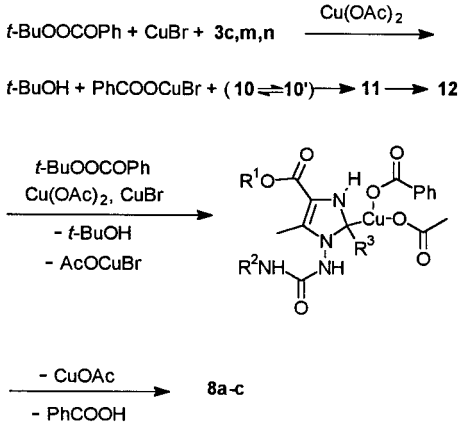
Similarly the formation of imidazole **8** (Scheme 5) is believed to involve the same intermediates **10**,**11** and the corresponding imidazolidine **12**, from which 2-imidazoline **6** is obtained by loss of copper(I) acetate and benzoic acid. Further, *t*-butyloxy radical promoted oxidation of compound **6** would then produce the imidazole **8**.

The behaviour[26] of compounds **3c**,**m**,**n** in the copper mediated radical reactions could be related to the electronic structure of the radicals **10**/**10′**, stabilised by resonance and electrophilic in character, which easily accomplish the subsequent cyclisation reaction by electrophilic addition to the carbon–nitrogen double bond. The copper promoted reactions of α-benzylamino hydrazone **3p** and α-propargyl-aminohydrazones **3i**–**l** very likely involve the same intermediates **10**/**10′** giving rise, starting from **3p**, to the 2-oxo-1,4-diazadiene **9** via an oxidative pathway much faster than the competitive cyclisation process, and, starting from **3i**–**l**, to a more complex reaction mixture. The behaviour of **3i**–**l** compared to **3p** could be related to the different thermochemical stabilisation energy of the intermediate propargyl and benzyl radicals.

In conclusion, the base promoted reactions of easily accessible α-aminohydrazones represent a simple and efficient method for the preparation of both 1-substituted and 1-unsubstituted 4-aminocarbonyl-1*H*-pyrazol-5(2*H*)-ones. The copper promoted reactions of the same α-amino hydrazones provide a divergent facile regiocontrolled



Scheme 4.



Scheme 5.

synthesis of the imidazoline/imidazole ring system. The copper promoted reaction of the α-benzylamino hydrazone produces a 2-imino-4-hydrazono-butirric acid derivative. Finally, the imidazolines can be easily hydrolysed to α-ketohydrazones.

3. Experimental

3.1. General

Melting points were uncorrected. ^{1}H NMR spectra were recorded at 200 or at 300 MHz and ^{13}C NMR at 50.3 or at 75.4 MHz. Mass spectra were carried out at an ionizing voltage of 70 eV. IR spectra were recorded in KBr dispersions unless otherwise stated. All starting materials, catalysts, ligands, bases, and solvents (anhydrous solvents included), are commercially available and were used as purchased, without further purification. PE is petroleum ether, bp 40–60°C. 1,2-Diaza-1,3-butadienes **1a–d** were prepared according to previously reported procedures.[27] Analytical and spectral data of α-ketohydrazones **7a–d** are reported in Ref. 22.

3.1.1. α-Aminohydrazones 3a–p. To a well-stirred solution of amines **2c**, **d** (1 mmol) in methanol (3 ml), or amines hydrochlorides **2a**,**b**,**e** (1 mmol) and sodium acetate trihydrate (1 mmol) in methanol (3 ml), a solution of the appropriate 1,2-diaza-1,3-butadienes **1a–d** (1 mmol) in THF (3 ml) was added dropwise. The mixture was stirred at room temperature until the azoalkene disappeared (TLC, 0.5–4 h), then poured in water (150 ml) and extracted twice with ethyl acetate. The organic layer was dried over Na_2SO_4, evaporated to dryness and the crude product purified by crystallisation or by flash chromatography eluting with PE/EtOAc mixtures.

3a: Purified by crystallisation (EtOAc/PE); white solid; mp 123.2–124.1°C; IR cm^{-1}: 3460, 3320, 3200, 1740, 1720, 1695, 1680, 1580; ^{1}H NMR $CDCl_3$ δ 1.17 (t, 7 Hz, 3H), 1.85 (s, 3H), 2.37 (s, 3H), 3.36 (s, 2H), 3.63 (s, 3H), 4.06 (q, 7 Hz, 2H), 4.19 (s, 1H), 6.12 (brs, 2H, D_2O-exch.), 9.34 (s, 1H, D_2O-exch.); ^{13}C NMR $CDCl_3$ δ 13.93, 14.03, 39.64, 51.31, 54.09, 59.91, 71.84, 145.03, 156.92, 170.23, 170.43. Anal. Calcd for $C_{11}H_{20}N_4O_5$: C, 45.82; H, 6.99; N, 19.43. Found: C, 45.79; H, 6.95; N, 19.48.

3b: Purified by crystallisation (EtOAc/PE); white solid; mp 131–133°C; IR cm^{-1} 3450, 3320, 3180, 1740, 1725, 1690, 1660, 1570; ^{1}H NMR $CDCl_3$ δ 1.17 (t, 7 Hz, 6H), 1.85 (s, 3H), 2.37 (s, 3H), 3.36 (s, 2H), 4.00–4.13 (m, 4H), 4.15 (s, 1H), 6.14 (brs, 2H, D_2O-exch.), 9.37 (s, 1H, D_2O-exch.); ^{13}C NMR $CDCl_3$ δ 14.00, 14.07, 14.13, 39.73, 54.10, 59.95, 60.12, 71.95, 145.20, 157.03, 169.74, 172.51. Anal. Calcd for $C_{12}H_{22}N_4O_5$: C, 47.67; H, 7.33; N, 18.53. Found: C, 47.92; H, 7.52; N, 18.74.

3c: Purified by crystallisation (EtOAc/PE); white solid; mp 107.3–109.1°C; IR cm^{-1} 3380, 3180, 3080, 1750, 1700, 1590; ^{1}H NMR $CDCl_3$ δ 1.15 (t, 7 Hz, 3H), 1.92 (s, 3H), 2.40 (s, 3H), 3.40 (s, 2H), 3.69 (s, 3H), 4.06 (q, 7 Hz, 2H), 4.30 (s, 1H), 6.97–7.50 (m, 5H), 8.40 (s, 1H, D_2O-exch.), 9.85 (s, 1H, D_2O-exch.); ^{13}C NMR $CDCl_3$ δ 14.00, 14.06, 39.70, 51.45, 54.3, 59.89, 71.82, 118.68 (2C), 122.48, 128.79 (2C), 138.63, 146.61, 152.84, 170.17, 170.43. Anal. Calcd for $C_{17}H_{24}N_4O_5$: C, 56.03; H, 6.64; N, 15.38. Found: C, 56.28; H, 6.91; N, 15.46.

3d: Purified by crystallisation (EtOAc/PE); white solid; mp 94.5–95.5°C; IR cm^{-1} 3375, 3180, 3080, 1750, 1700, 1590; ^{1}H NMR $CDCl_3$ δ 1.12–1.24 (m, 6H), 1.92 (s, 3H), 2.41 (s, 3H), 3.40 (s, 2H), 4.04–4.22 (m, 4H), 4.26 (s, 1H), 7.01–7.49 (m, 5H), 8.39 (s, 1H, D_2O-exch.), 9.83 (s, 1H, D_2O-exch.); ^{13}C NMR $CDCl_3$ δ 14.00, 14.09 (2C), 39.76, 54.23, 59.89, 60.20, 71.81, 118.68 (2C), 122.46, 128.79 (2C), 138.58, 146.66, 152.84, 169.59, 170.43. Anal. Calcd for $C_{18}H_{26}N_4O_5$: C, 57.13; H, 6.92; N, 14.81. Found: C, 57.46; H, 7.18; N, 14.67.

3e: Purified by crystallisation (EtOAc/PE); white solid; mp 123.3–124.4°C; IR cm^{-1} 3480, 3310, 3190, 1750, 1725, 1680, 1630, 1575; ^{1}H NMR $CDCl_3$ δ 1.17 (t, 7 Hz, 3H), 1.75 (s, 3H), 2.90 (brs, 1H, D_2O-exch.), 3.28 (s, 2H), 3.86 (s, 3H), 4.01–4.12 (m, 3H), 6.32 (brs, 2H, D_2O-exch.), 9.30 (s, 1H, D_2O-exch.); ^{13}C NMR $CDCl_3$ δ 13.02, 14.06, 47.77, 52.08, 60.09, 66.32, 147.47, 157.23, 171.10, 171.67. Anal. Calcd for $C_{10}H_{18}N_4O_5$: C, 43.79; H, 6.61; N, 20.43. Found: C, 44.06; H, 6.94; N, 20.23.

3f: Purified by crystallisation (EtOAc/PE); white solid; mp 79.2–83.2°C; IR cm$-^1$ 3480, 3310, 3190, 1750, 1725, 1680, 1630, 1575; ^{1}H NMR $CDCl_3$ δ 1.17 (t, 7 Hz, 6H), 1.75 (s, 3H), 2.88 (brs, 1H, D_2O-exch.), 3.28 (s, 2H), 3.97–4.14 (m, 5H), 6.32 (brs, 2H, D_2O-exch.), 9.28 (s, 1H, D_2O-exch.); ^{13}C NMR $CDCl_3$ δ 12.96, 14.01 (2C), 47.73, 60.04, 60.75, 66.34, 144.45, 157.18, 170.52, 171.64. Anal. Calcd for $C_{11}H_{20}N_4O_5$: C, 45.82; H, 6.99; N, 19.43. Found: C, 46.17; H, 7.12; N, 19.26.

3g: Purified by crystallisation (EtOAc/PE); white solid; mp 78.1–82.2°C; IR cm^{-1} 3300, 3180, 1725, 1640, 1590; ^{1}H NMR $CDCl_3$ δ 1.17 (t, 7 Hz, 3H), 1.82 (s, 3H), 2.89 (brs, 1H, D_2O-exch.), 3.34 (s, 2H), 3.70 (s, 3H), 4.02–4.14 (m, 3H), 6.96–7.58 (m, 5H), 8.70 (s, 1H, D_2O-exch.), 9.72 (s, 1H, D_2O-exch.); ^{13}C NMR $CDCl_3$ δ 13.16, 14.00, 47.84, 52.15, 60.06, 66.27, 119.26 (2C), 122.41, 128.56 (2C), 138.92, 140.06, 153.22, 170.98, 171.70. Anal. Calcd for

$C_{16}H_{22}N_4O_5$: C, 54.84; H, 6.33; N, 15.99. Found: C, 54.72; H, 6.26; N, 15.87.

3h: Purified by crystallisation (EtOAc/PE); white solid; mp 100.0–101.6°C; IR cm^{-1} 3360, 3190, 1740, 1700, 1590; ^1H NMR $CDCl_3$ δ 1.12–1.23 (m, 6H), 1.83 (s, 3H), 2.99 (brs, 1H, D_2O-exch.), 3.35 (s, 2H), 4.02–4.19 (m, 5H), 7.00–7.59 (m, 5H), 8.72 (s, 1H, D_2O-exch.), 9.73 (s, 1H, D_2O-exch.); ^{13}C NMR $CDCl_3$ δ 13.16, 14.00 (2C), 47.82, 60.06, 60.87, 66.30, 119.26 (2C), 122.38, 128.56 (2C), 138.92, 146.09, 153.22, 170.43, 171.70. Anal. Calcd for $C_{17}H_{24}N_4O_5$: C, 56.03; H, 6.64; N, 15.38. Found: C, 55.84; H, 6.48; N, 15.43.

3i: Purified by crystallisation (diisopropylether/isopropanol); white solid; mp 148.0–149.9°C; IR cm^{-1} 3472, 3328, 3286, 3200, 1736, 1670, 1576; ^1H NMR $CDCl_3$ δ 1.84 (s, 3H), 2.24 (t, 2 Hz, 1H), 2.32 (brs, 1H, D_2O-exch.), 3.33 (dd, 2, 17 Hz, 1H), 3.48 (dd, 2, 17 Hz, 1H), 3.78 (s, 3H), 4.19 (s, 1H), 4.85 (brs, 1H, D_2O-exch.), 5.95 (brs, 1H, D_2O-exch.), 7.81 (brs, 1H, D_2O-exch.); ^{13}C NMR DMSO-d_6 δ 13.59, 35.80, 52.21, 65.93, 74.11, 82.30, 144.53, 157.37, 171.39. Anal. Calcd for $C_9H_{14}N_4O_3$: C, 47.78; H, 6.24; N, 24.77. Found: C, 47.56; H, 6.04; N, 24.85.

3j: Purified by crystallisation (diisopropylether/isopropanol); white solid; mp 123–124°C; IR cm^{-1} 3464, 3338, 3232, 2100, 1738, 1694, 1572; ^1H NMR $CDCl_3$ δ 1.28 (t, 7 Hz, 3H), 1.86 (s, 3H), 2.23 (t, 2 Hz, 1H), 2.25 (brs, 1H, D_2O-exch.), 3.32 (dd, 2, 17 Hz, 1H), 3.46 (dd, 2, 17 Hz, 1H), 4.15 (s, 1H), 4.24 (q, 7 Hz, 2H), 5.30 (brs, 1H, D_2O-exch.), 5.95 (brs, 1H, D_2O-exch.), 8.62 (brs, 1H, D_2O-exch.); ^{13}C NMR $CDCl_3$ δ 13.71, 14.82, 36.46, 62.03, 66.25, 72.74, 81.93, 146.12, 158.25, 171.53. Anal. Calcd for $C_{10}H_{16}N_4O_3$: C, 49.99; H, 6.71; N, 23.32. Found: C, 49.71; H, 6.57; N, 23.06.

3k: Purified by crystallisation (diisopropylether/isopropanol); white solid; mp 120.8–121.8°C; IR cm^{-1} 3310, 3300, 1740, 1672, 1594; ^1H NMR $CDCl_3$ δ 1.94 (s, 3H), 2.18 (brs, 1H, D_2O-exch.), 2.28 (t, 2 Hz, 1H), 3.38 (dd, 2, 17 Hz, 1H), 3.51 (dd, 2, 17 Hz, 1H), 3.80 (s, 3H), 4.26 (s, 1H), 7.07–7.51 (m, 5H), 8.15 (brs, 1H, D_2O-exch.), 8.65 (brs, 1H, D_2O-exch.); ^{13}C NMR $CDCl_3$ δ 13.63, 36.74, 53.04, 66.56, 72.70, 81.48, 119.80 (2C), 123.77, 129.39 (2C), 138.53, 146.67, 154.39, 171.62. Anal. Calcd for $C_{15}H_{18}N_4O_3$: C, 59.59; H, 6.00; N, 18.53. Found: C, 59.36; H, 5.76; N, 18.75.

3l: Purified by crystallisation (diisopropylether/isopropanol); white solid; mp 101.4–101.9°C; IR cm^{-1} 3312, 3296, 1736, 1674, 1594, 1540; ^1H NMR $CDCl_3$ δ 1.30 (t, 7 Hz, 3H), 1.95 (s, 3H), 2.20 (brs, 1H, D_2O-exch.), 2.27 (t, 2 Hz, 1H), 3.37 (dd, 2, 17 Hz, 1H), 3.51 (dd, 2, 17 Hz, 1H), 4.24 (s, 1H), 4.26 (q, 7 Hz, 2H), 7.03–7.52 (m, 5H), 8.15 (brs, 1H, D_2O-exch.), 8.69 (brs, 1H, D_2O-exch.); ^{13}C NMR $CDCl_3$ δ 13.72, 14.66, 36.71, 62.17, 66.62, 72.66, 81.58, 119.78 (2C), 123.71, 129.36 (2C), 138.59, 146.85, 154.54, 171.12. Anal. Calcd for $C_{16}H_{20}N_4O_3$: C, 60.74; H, 6.37; N, 17.71. Found: C, 60.52; H, 6.24; N, 17.85.

3m: Purified by flash chromatography (EtOAc/PE, 8:2); white solid; mp 121–122°C; IR cm^{-1} 3538, 3420, 3348, 1726, 1700, 1560; ^1H NMR DMSO-d_6 δ 1.19 (t, 7 Hz, 3H), 1.77 (s, 3H), 3.58 (m, 3H; after D_2O exch.: s, 2H), 3.98 (d, 7 Hz, 1H; after D_2O exch.: s, 1H), 4.14 (q, 7 Hz, 2H), 6.38 (brs, 2H, D_2O-exch.), 9.28 (brs, 1H, D_2O-exch.); ^{13}C NMR DMSO-d_6 δ 14.05, 14.75, 35.49, 61.64, 66.96, 119.52, 144.09, 157.76, 170.75. Anal. Calcd for $C_9H_{15}N_5O_3$: C, 44.80; H, 6.27; N, 29.03. Found: C, 44.61; H, 6.18; N, 29.38.

3n: Purified by flash chromatography (EtOAc/PE, 7:3); white solid; mp 94.8–95.1°C; IR cm^{-1} 3352, 3204, 1740, 1704, 1594; ^1H NMR $CDCl_3$ δ 1.94 (s, 3H), 2.52 (brs, 1H, D_2O-exch.), 3.50 (dd, 7, 17 Hz, 1H; after D_2O exch.: d, 17 Hz), 3.73 (d, 17 Hz, 1H), 3.82 (s, 3H), 4.25 (s, 1H), 7.04–7.53 (m, 5H), 8.14 (brs, 1H, D_2O-exch.), 8.94 (brs, 1H, D_2O-exch.); ^{13}C NMR $CDCl_3$ δ 13.48, 35.57, 53.42, 66.68, 117.66, 119.92 (2C), 123.92, 129.42 (2C), 138.38, 145.44, 154.53, 170.76. Anal. Calcd for $C_{14}H_{17}N_5O_3$: C, 55.43; H, 5.65; N, 23.09. Found: C, 55.25; H, 5.47; N, 23.27.

3o: Purified by flash chromatography (EtOAc/PE, 7:3); white solid; mp 119.6–121.1°C; IR cm^{-1} 3354, 3204, 1734, 1594, 1534; ^1H NMR DMSO-d_6 δ 1.20 (t, 7 Hz, 3H), 1.84 (s, 3H), 3.64 (m, 3H; after D_2O exch.: s, 2H), 4.12–4.23 (m, 3H), 6.93–7.58 (m, 5H), 8.79 (brs, 1H, D_2O-exch.), 9.79 (brs, 1H, D_2O-exch.); ^{13}C NMR DMSO-d_6 δ 14.27, 14.73, 35.51, 61.75, 66.98, 119.57, 120.18 (2C), 123.24, 129.32 (2C), 139.65, 145.89, 153.99, 170.67. Anal. Calcd for $C_{15}H_{19}N_5O_3$: C, 56.77; H, 6.03; N, 22.07. Found: C, 56.58; H, 5.74; N, 21.83.

3p: Purified by flash chromatography (EtOAc/PE, 9:1); colourless oil; IR cm^{-1} 3450, 3320, 1740, 1704, 1680; ^1H NMR $CDCl_3$ δ 1.86 (s, 3H), 2.31 (brs, 1H, D_2O-exch.), 3.72 (s, 2H), 3.73 (s, 3H), 3.97 (s, 1H), 5.45 (brs, 1H, D_2O-exch.), 5.95 (brs, 1H, D_2O-exch.) 7.30 (m, 5H), 8.70 (s, 1H, D_2O-exch.); ^{13}C NMR DMSO-d_6 δ 13.96, 51.25, 52.62, 67.10, 127.46, 128.82 (2C), 128.86 (2C), 140.82, 145.66, 157.87, 172.19; MS *m/z* 278 (10) [M^+], 219 (90), 202 (100), 187 (41), 178 (32), 91 (70).

3.1.2. 1-Aminocarbonyl-1*H*-pyrazol-5(2*H*)ones 4a–e. To a well-stirred solution of the appropriate α-aminohydrazones **3a–d,g,h** and **3i–l** (1 mmol) in dry THF/EtOH (2 ml/2 ml), NaH (24 mg, 1 mmol) was added portionwise over a period of 10 min. The reaction mixture was then stirred at room temperature for 5–30 min. Pyrazolones **4d,e** were collected by filtration from the reaction mixture, washed with dry THF and then dried under vacuum. The reaction mixtures containing crude pyrazolones **4a–c** were evaporated to dryness and the residue was dissolved in EtOAc (15 ml) and treated with CF_3COOH to pH 5 and then washed twice with water. The organic layer, dried over Na_2SO_4, was evaporated and the residue purified by crystallisation (pyrazolones **4b,c**) or by flash chromatography (pyrazolone **4a**).

4a: Purified by flash chromatography (EtOAc); colourless oil; IR cm^{-1} 3280, 1740, 1720, 1700, 1660, 1620, 1570; ^1H NMR $CDCl_3$ δ 1.14 (t, 7 Hz, 3H), 2.13 (s, 3H), 2.68 (s, 3H), 3.72 (s, 2H), 4.04 (q, 7 Hz, 2H), 7.69 (brs, 1H, D_2O-exch.), 8.25 (brs, 1H, D_2O-exch.), 11.69 (s, 1H, D_2O-exch.); ^{13}C NMR $CDCl_3$ δ 10.05, 13.94, 42.32, 55.97, 59.69, 115.48, 145.78, 149.23, 159.77, 170.44.

4b: Purified by crystallisation (EtOAc/PE); white solid; mp 101.1–103.2°C; IR cm^{-1} 3312, 3296, 1736, 1674, 1594, 1540; ^1H NMR $CDCl_3$ δ 1.18 (t, 7 Hz, 3H), 2.23 (s, 3H), 2.76 (s, 3H), 3.80 (s, 2H), 4.07 (q, 7 Hz, 2H), 7.12–7.59 (m, 5H), 11.28 (s, 1H, D_2O-exch.), 12.23 (brs, 1H, D_2O-exch.). ^{13}C NMR $CDCl_3$ δ 10.11, 13.88, 42.26, 55.92, 59.70, 115.32, 119.49 (2C), 123.85, 129.03 (2C), 136.92, 146.34, 146.79, 159.99, 170.25. Anal. Calcd for $C_{16}H_{20}N_4O_4$: C, 57.82; H, 6.06; N, 16.86. Found: C, 57.65; H, 5.88; N, 16.95.

4c: Purified by crystallisation (EtOAc/PE); white solid; mp 150.1–154.3°C; IR cm^{-1} 3215, 3135, 3055, 1760, 1715, 1600 1570; ^1H NMR $CDCl_3$ δ 1.17 (t, 7 Hz, 3H), 2.16 (s, 3H), 3.62–3.74 (m, 3H), 4.06 (q, 7 Hz, 2H), 7.08–7.56 (m, 5H), 11.26 (s, 1H, D_2O-exch.), 11.40 (s, 1H, D_2O-exch.); ^{13}C NMR $CDCl_3$ δ 9.94, 13.95, 47.34, 59.86, 114.01, 119.48 (2C), 123.83, 129.03 (2C), 137.03, 141.21, 146.40, 159.43, 171.78. Anal. Calcd for $C_{15}H_{18}N_4O_4$: C, 56.59; H, 5.70; N, 17.60. Found: C, 56.37; H, 5.53; N, 17.54.

4d: Pale yellow solid; mp 177°C (dec.); IR cm^{-1} 3438, 3344, 3260, 3112, 1686, 1620, 1570; ^1H NMR DMSO-d_6 δ 1.94 (s, 3H), 2.67 (brs, 1H, D_2O-exch.), 2.88 (t, 2 Hz, 1H), 3.45 (d, 2 Hz, 2H), 6.72 (brs, 1H, D_2O-exch.), 9.49 (brs, 1H, D_2O-exch.); ^{13}C NMR DMSO-d_6 δ 12.93, 73.10, 81.47, 86.23, 111.91, 149.82, 153.98, 158.39; MS *m/z* 194 (10) [M^+], 166 (41), 151 (75), 129 (45), 124 (68), 105 (100). Anal. Calcd for $C_8H_{10}N_4O_2$: C, 49.48; H, 5.19; N, 28.85. Found: C, 49.16; H, 4.88; N, 28.66.

4e: Pale yellow solid; mp 243°C (dec.); IR cm^{-1} 3226, 1706, 1636, 1622, 1596, 1574; ^1H NMR DMSO-d_6 δ 1.99 (s, 3H), 2.80 (brs, 1H, D_2O-exch.), 2.92 (t, 2 Hz, 1H), 3.51 (d, 2 Hz, 2H), 6.96–7.55 (m, 5H), 13.11 (brs, 1H, D_2O-exch.); ^{13}C NMR DMSO-d_6 δ 13.02, 72.96, 81.48, 86.27, 111.42, 119.16 (2C), 119.32, 129.15 (2C), 139.66, 149.56, 153.92, 159.61; MS *m/z* 270 (8) [M^+], 236 (15), 176 (13), 149 (47), 119 (100). Anal. Calcd for $C_{14}H_{14}N_4O_2$: C, 62.21; H, 5.22; N, 20.73. Found: C, 61.93; H, 5.59; N, 20.48.

3.1.3. 1*H*-Pyrazol-5(2*H*)one 5a. A well-stirred solution of pyrazolone **4a** (256.3 mg, 1 mmol) in ethanol (5 ml) was heated under reflux for 1 h. The reaction mixture was then evaporated to dryness and the crude purified by chromatography over silica gel (cyclohexane/EtOAc, 4:6) and finally by crystallisation from Et_2O/PE. Yield 65%; white solid; mp 121.3–124.1°C; IR cm^{-1} 3440, 2640, 1615, 1580, 1540; ^1H NMR DMSO-d_6 δ 1.15 (t, 7 Hz, 3H), 2.06 (s, 3H), 2.66 (s, 3H), 3.62 (s, 2H), 4.03 (q, 7 Hz, 2H), 10.17 (brs, 2H, D_2O-exch.); ^{13}C NMR DMSO-d_6 δ 9.70, 14.02, 42.91, 57.41, 59.66, 114.81, 133.78, 156.57, 170.86. Anal. Calcd for $C_9H_{15}N_3O_3$: C, 50.69; H, 7.09; N, 19.71. Found: C, 50.55; H, 6.88; N, 19.38.

3.1.4. Alkyl 3,5-dimethyl-1-ureido-2,3-dihydro-1*H*-imidazoles-2,4-dicarboxylates 6a,b. To a solution of the appropriate α-aminohydrazones **3a** or **3b** (1 mmol) in dry THF (5 ml) CuI (190 mg, 1 mmol) was added. The mixture was then purged with oxygen, connected to a balloon of oxygen and stirred at room temperature for 1 h. Dihydroimidazoles **6a**,**b** were collected by filtration, washed twice with dry THF and recrystallised from EtOAc/Et_2O.

6a: White solid; mp 151–153°C; IR cm^{-1} 3425, 3460, 1740, 1730, 1685, 1670; ^1H NMR $CDCl_3$ δ 1.27 (t, 7 Hz, 3H), 1.91 (s, 3H), 2.83 (s, 3H), 3.89 (s, 3H), 4.20 (q, 7 Hz, 2H), 4.42 (s, 1H), 4.50–6.50 (brs, 2H, D_2O-exch.), 5.55 (brs, 1H, D_2O-exch.); ^{13}C NMR DMSO-d_6 δ 13.92, 18.11, 34.74, 53.20, 60.53, 64.24, 81.84, 141.27, 155.20, 168.01, 170.52; MS *m/z* 286 (4) [M^+], 285 (14), 229 (100), 186 (97), 126 (93), 100 (57). Anal. Calcd for $C_{11}H_{18}N_4O_5$: C, 46.14; H, 6.33; N, 19.57. Found: C, 46.03; H, 6.28; N, 19.58.

6b: White solid; mp 157–159°C; IR cm^{-1} 3425, 3460, 1743, 1720, 1680, 1670; ^1H NMR $CDCl_3$ δ 1.32 (m, 6H), 1.90 (s, 3H), 2.63 (s, 3H), 3.89 (s, 3H), 4.24 (m, 4H), 4.41 (s, 1H), 5.10 (brs, 1H, D_2O-exch.), 5.52 (brs, 1H, D_2O-exch.), 6.05 (brs, 1H, D_2O-exch.); ^{13}C NMR DMSO-d_6 δ 13.94, 14.06, 18.16, 34.77, 53.26, 60.54, 62.56, 81.92, 143.36, 154.91, 163.01, 172.65; MS *m/z* 300 (12) [M^+], 299 (15), 243 (87), 200 (100), 140 (82), 114 (45). Anal. Calcd for $C_{12}H_{20}N_4O_5$: C, 47.99; H, 6.71; N, 18.65. Found: C, 47.85; H, 6.68; N, 18.76.

3.1.5. 2-Ketohydrazones 7a–d. From 4,5-dihydroimidazoles **6a**,**b**: a solution of **6a** or **6b** (1 mmol) in MeOH/H_2O 2:1 (10 ml) was stirred at room temperature for 1 h. The solvent was then removed under reduced pressure and the crude product crystallised from methanol yielding pure **7a**,**b**. For analytical and spectral data see Ref. 22. From 2-ketohydrazones **3c**–**h**: the crude reaction mixture obtained as reported for the 4,5-dihydroimidazoles **6a**,**b** was poured into HCl 0.1 M (60 ml) and extracted twice with ethyl acetate. The organic layer, dried over Na_2SO_4, was evaporated to dryness and the crude purified by crystallisation from methanol (**7a**,**b**) or by flash cromatography (**7c**,**d**) eluting with ethyl acetate/PE mixtures. For analytical and spectral data see Ref. 22.

3.1.6. Alkyl 5-methyl-1-ureidoimidazole-4-carboxylates 8a–c. To a nitrogen flushed solution of the appropriate α-aminohydrazones **3c**,**m**,**n** (1 mmol) in dry THF (5 ml) CuBr (157.8 mg, 1.1 mmol), $Cu(OAc)_2$ (199.8 mg, 1.1 mmol) and *t*-BuOOCOPh (388.4 mg, 2 mmol) were added. The mixture was stirred for 3 h at 60°C, then poured in $NaHCO_3$ (sat. sol. 50 ml) and extracted twice with EtOAc. The organic layer, dried over Na_2SO_4, was evaporated to dryness and the crude product purified by flash chromatography over silica gel. Elution with PE/ethyl acetate mixtures afforded pure **8a**–**c**.

8a: White solid; mp 189–191°C; IR cm^{-1} 3335, 3210, 2260, 1740, 1725, 1695, 1610, 1560; ^1H NMR $CDCl_3$ δ 1.16 (t, 7 Hz, 3H), 2.46 (s, 3H), 3.82 (s, 3H), 4.17 (q, 7 Hz, 2H), 7.06–7.52 (m, 5H), 8.93 and 9.52 (brs, 1H, D_2O-exch.); ^{13}C NMR $CDCl_3$ δ 13.82, 29.66, 51.96, 62.31, 119.73 (2C), 123.61, 126.49, 128.84 (2C), 136.15, 137.92, 142.55, 154.31, 157.14, 163.25; MS *m/z* 346 (50) [M^+], 227 (77), 195 (75), 155 (58), 119 (100). Anal. Calcd for $C_{16}H_{18}N_4O_5$: C, 55.48; H, 5.23; N, 16.17. Found: C, 55.43; H, 5.21; N, 16.23.

8b: White solid; mp 196–198°C; IR cm^{-1} 3520, 3420, 3350, 2245, 1725, 1690, 1610, 1565; ^1H NMR DMSO-d_6 δ 1.32 (t, 7 Hz, 3H), 2.38 (s, 3H), 4.27 (q, 7 Hz, 2H), 6.85 (brs, 2H, D_2O-exch.), 9.98 (brs, 1H, D_2O-exch.); ^{13}C NMR DMSO-d_6

9.57, 14.41, 60.58, 110.46, 122.52, 128.64, 141.46, 156.07, 161.62; MS *m/z* 237 (25) [M^+], 179 (100), 138 (45). Anal. Calcd for $C_9H_{11}N_5O_3$: C, 45.56; H, 4.67; N, 29.52. Found: C, 45.55; H, 4.68; N, 29.48.

8c: White solid; mp 170–172°C; IR cm^{-1} 3315, 3220, 3150, 2245, 1725, 1700, 1600, 1550; ^1H NMR $CDCl_3$ δ 2.57 (s, 3H), 4.00 (s, 3H), 7.30–7.65 (m, 5H), 8.79 and 10.65 (brs, 1H, D_2O-exch.); ^{13}C NMR $CDCl_3$ δ 10.05, 52.68, 108.46, 119.49 (2C), 123.34, 128.91, 129.09 (2C), 133.67, 137.95, 142.18, 152.71, 163.66; MS *m/z* 299 (35) [M^+], 180 (86), 148 (85), 119 (100). Anal. Calcd for $C_{14}H_{13}N_5O_3$: C, 56.18; H, 4.37; N, 23.40. Found: C, 56.16; H, 4.34; N, 23.47.

3.1.7. 3-Aminocarbonylhydrazono-2-benzylimino-butirric acid methyl ester 9. The crude reaction product obtained as reported for imidazoles **8** was purified by flash chromatography. Elution with EtOAC/PE 60:40 yields pure **9**. Mp 129–131°C; IR cm^{-1} 3458, 3372, 3212, 1742, 1698, 1582; ^1H NMR $CDCl_3$ δ 2.12 (s, 3H), 3.89 (s, 3H), 4.64 (s, 2H), 5.35 and 5.90 (brs, 1H, D_2O-exch.), 7.33 (m, 5H), 8.85 (brs, 1H, D_2O-exch.); ^{13}C NMR $CDCl_3$ δ 10.67, 52.33, 59.06, 127.70, 128.36 (2C), 128.99 (2C), 138.72, 145.92, 157.85, 161.11, 166.12; MS *m/z* 276 (2) [M^+], 275 (7), 232 (40), 216 (65), 199 (37), 185 (100). Anal. Calcd for $C_{13}H_{16}N_4O_3$: C, 56.50; H, 5.83; N, 20.28. Found: C, 56.45; H, 5.79; N, 20.23.

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