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Heterocycles from Morita–Baylis–Hillman adducts: synthesis of 5-oxopyrazolidines, arylidene-5-oxopyrazolidines, and oxo-2,5-dihydro-pyrazols

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ABSTRACT

Starting from Morita–Baylis–Hillman (MBH) adducts, an approach for the synthesis of oxopyrazolidines, arylidene-oxopyrazolidines, and oxo-2,5-dihydropyrazoles is described. The method is based on a tandem process involving a Michael addition of amino-guanidine into silylated and acetylated MBH adducts, followed by intramolecular cyclization. The use of acetylated MBH adducts led also to the synthesis of unusual pyrazoles, which is facilitated by an unexpected base-mediated equilibrium.

1. Introduction

Heterocycles form the most basic building blocks of life playing also a key role in several segments of the chemical industry. They are also important monomers for polymers and moieties of biologically active compounds, such as agrochemicals and drugs.[1] A large amount of additives and modifiers used in different segments of chemical industry, such as cosmetics, reprographic, plastics, and information storage are also heterocyclic in their constitution.[1c] Owing to the vast commercial and biological relevance of heterocycles in organic chemistry, many methodologies are available for their preparation.[1a,b]

Pyrazolones and pyrazolidinones are common heterocycles with a great diversity of biological properties.[2] For instance, they exhibited analgesic, antibacterial, and antifungal activities (**1** and **2**, Fig. 1),[3] as well as anti-tumoral activity[4] and anti-ischemic effect.[5] Recently, pyrazolones **3** and **4** (Fig. 1) were identified as HIV-integrase inhibitors, which constitutes a new class of antiretroviral agents.[6]

The synthetic utility and biological activity of pyrazolidinones have also raised interest on these compounds in the last decade.[7] They have been used as templates in enantioselective Diels–Alder,[8] Michael,[9] and click reactions.[10] Pyrazolidinones are also present in some bicyclic antibiotics developed by Eli Lilly (Fig. 1, compounds **5**, **6**, and **7**) some years ago.[11]

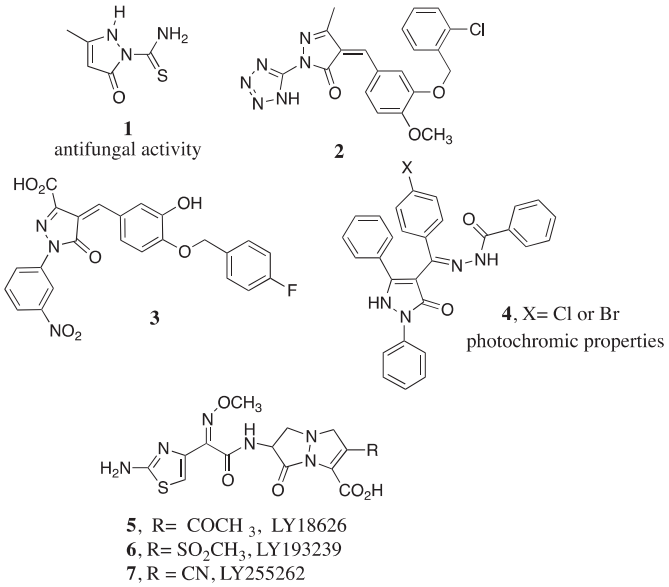

Fig. 1. Some representative examples of biologically active pyrazolones and pyrazolidinones.

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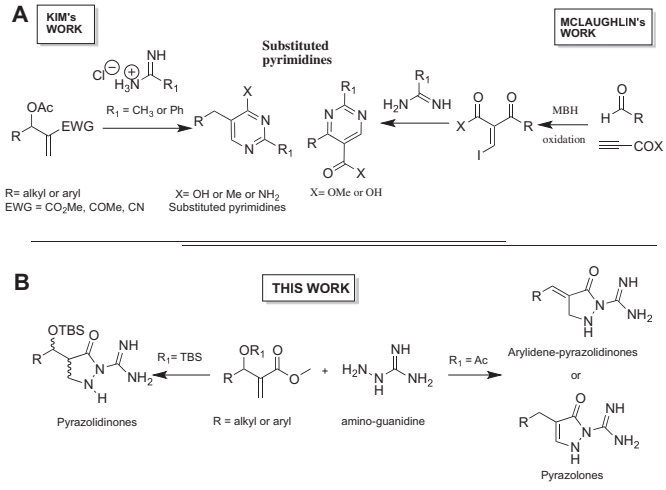
The presence of both pyrazolone and pyrazolidinone units in many molecules of pharmaceutical interest has also led to the development of a great variety of methods for their preparation.

The most classic approach to prepare pyrazolones is via the reaction between a β-ketoester, a β-cyanoester or α,β-unsaturated esters and hydrazine or hydrazine derivatives (alkyl, aryl or heterocyclic).[12] Recently, Ma et al.[13] reported on a one-pot synthesis of arylidene-pyrazolones by treatment of a mixture of ethyl acetoacetate, electrodeficient phenyl-hydrazines and electron poor aromatic aldehydes in the presence of microwaves. Alternatively, palladium can be used as catalyst for the preparation of pyrazolones from 1,2-diaza-1,3-butadienes.[14] Organocatalyzed methodologies for the synthesis of pyrazolones have also been reported recently.[15]

Most methods for the preparation of pyrazolidinones rely on [3+2] cycloadditions using dipoles, such as diazoalkanes,[16] nitrile imines,[17] azomethine[18] or hydrazones.[19] Metal-catalyzed amination of allenes is also used as an alternative methodology to obtain pyrazolidinones or pyrazolidines.[20] Recently, oxo-ketenes were used as substrate for [1,3]dipolar cycloaddition with hydrazones.[21] Addition of substituted hydrazines to α,β-unsaturated esters has also been used as approach to prepare pyrazolidinones.[19]

The Morita–Baylis–Hillman (MBH) reaction[22,23] is a versatile chemical transformation that provides small poly-functionalized molecules, which can be used as Michael acceptors in the preparation of a great diversity of molecules.[24]

Recently, Kim et al.[25] and McLaughlin et al.[26] have independently investigated the chemical behavior of MBH adducts as substrates for a reaction with amidine. These reactions gave the respective substituted pyrimidines or 2,5-substituted pyrimidine carboxylate as main products in good yields (Scheme 1).



Scheme 1. Kim's and McLaughlin's syntheses of substituted pyrimidines and our approach to the synthesis of pyrazolones and pyrazolidinones both from Morita–Baylis–Hillman adducts.

These results associated with our interest in preparing some pyrazolones and pyrazolidinones for biological screening against some strains of human cancer cells stimulated us to investigate the chemical behavior of amino-guanidine in the presence of silylated and acetylated MBH adducts. Curiously, guanidine has already been used as catalyst for the MBH reaction,[27] but this bis-nucleophile or their derivatives have never been investigated as reagent in a Michael addition with MBH adducts.

We have already demonstrated the influence of the silylated protecting groups in the diastereoselectivity of the Michael addition reaction on MBH adducts.[28] If this behavior is also observed here, it would be possible to control the relative stereochemistries of two stereogenic centers and form a new five-membered ring in a single step (Scheme 1, part B).

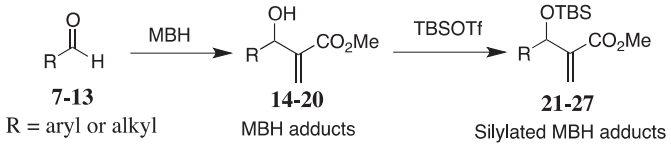
We therefore disclose herein a new, simple, and direct approach to the synthesis of pyrazolones and pyrazolidinones from MBH adducts. Our methodology uses a one-pot two step sequence involving a Michael addition of amino-guanidine, followed by intramolecular cyclization.

2. Results and discussion

The investigation was initiated by preparing some MBH adducts according to a method we described some years ago.[29] The adducts were then silylated in the presence of TBSOTf/NEt_3 to provide the corresponding silyl ethers in good to excellent overall yields (Table 1).

The silylated compounds were then diluted in MeOH and treated, under reflux, with aminoguanidine carbonate in the presence of triethylamine to give the substituted pyrazolidinones in good yields and diastereoselectivity varying from 2:1 to 7:1 after 3 h (Table 2).

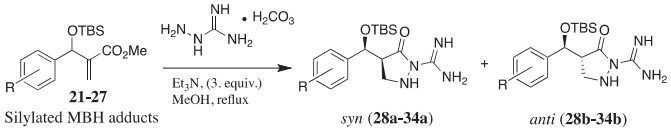
Table 1
MBH reaction and silylation



Entry	Aldehyde	MBH, yield (%)[a,b]	Silylation (%)[b]
1	R=4-NO_2Ph (**7**)	**14**, 97	**21**, 97
2	R=2-F–Ph (**8**)	**15**, 87	**22**, 94
3	R=3-Cl–Ph (**9**)	**16**, 91	**23**, >99
4	R=4-Cl–Ph (**10**)	**17**, 87	**24**, >99
5	R=4-*t*Bu–Ph (**11**)	**18**, 77	**25**, >99
6	R=4-MeO-Ph (**12**)	**19**, 72	**26**, >99
9	R=3,4-OCH_2O–Ph (**13**)	**20**, 73	**27**, >99

[a] The reactions were carried out using an excess of methyl acrylate (as solvent) and 0.65 equiv of DABCO at room temperature or in the presence of ultrasound radiation.
[b] Yields refer to isolated and purified products.

Table 2
Michael addition reaction with amino-guanidine



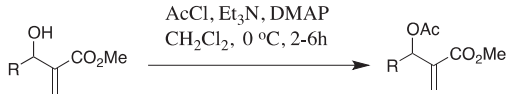
Entry	Silylated adduct	Yield (%)[a]	*syn*: *anti* ratio[b, c]
1	**21**, R=4-NO_2	**28a**/**b**, 83	2:1
2	**22**, R=2-F	**29a**/**b**, 81	7:1
3	**23**, R=3-Cl	**30a**/**b**, 78	5:1
4	**24**, R=4-Cl	**31a**/**b**, 88	4:1
5	**25**, R=4-*t*Bu	**32a**/**b**, 83	3:1
6	**26**, R=4-MeO	**33a**/**b**, 81	5:1
9	**27**, R=3,4-OCH_2–	**34a**/**b**, 83	2:1

[a] Yields refer to isolated and purified products.
[b] Determined by ^1H NMR of the crude reaction mixture.
[c] The relative stereochemistry was determined by measuring the coupling constant of the duplet attributed to the carbinolic hydrogen.

A wide range of MBH adducts are well tolerated, allowing the synthesis of a set of substituted pyrazolidinones in a tandem sequence. For all reactions, diastereoselectivity favored the *syn* diastereoisomers. These results are in accordance with previous observations made by us[28] and confirmed elsewhere.[30] Unfortunately, all chromatographic attempts to separate the diastereoisomers failed.

Further, a dichloromethane solution of the MBH adducts was treated with acetyl chloride in the presence of a catalytic amount of DMAP at 0 °C to afford the acetylated derivatives in good yields (Table 3).

Table 3
Acetylation of the MBH adducts



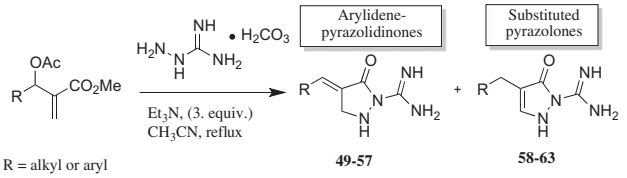
7-13, 35-38, R= alkyl or aryl MBH adducts — **38-48** acetylated MBH adducts

Entry	MBH adduct	Acetylated MBH, yield (%)[a]
1	**7**, R=4-NO_2–Ph	**38**, 93
2	**8**, R=2-F–Ph	**39**, 62
3	**9**, R=3-Cl–Ph	**40**, 92
4	**10**, R=4-Cl–Ph	**41**, 75
5	**11**, R=4-*t*Bu–Ph	**42**, 81
6	**12**, R=4-MeO–Ph	**43**, 95
7	**13**, R=3,4-OCH_2O–Ph	**44**, 75
8	**35**, R=4-MeO_2S–Ph	**45**, 85
9	**36**, R=Ph	**46**, 70
10	**37**, R=cyclohexyl	**47**, 74
11	**38**, R=3-NO_2–Ph	**48**, 70

[a] Yields refer to isolated and purified products.

The experimental protocol used with the silylated adducts was repeated to provide either arylidene pyrazolidinones[31] or pyrazolones with the exception that MeOH was replaced by acetonitrile (Table 4).

Table 4
Synthesis of arylidene pyrazolidinones and pyrazolones from acetylated MB



38-48, R = alkyl or aryl acetylated MBH adducts — **49-57** — **58-63**

Entry	Acetyl-MBH	Time (h)	Pyrazolidinones (%)[a]	Pyrazolones (%)[a]
1	**38**	12	—	**58**, 53
2	**39**	12	**49**, 30	
		24	—	**59**, 56
3	**40**	12	**50**, 53[b,d]	**60**, 5
4	**41**	12	**51**, 58[c,d]	**61**, 8
5	**42**	12	**52**, 45	
6	**43**	12	**53**, 65	
7	**44**	12	**54**, 76	
		48	**54**, 86	
8	**45**	12	—	**62**, 59
9	**46**	12	**55**, 65	—
10	**47**	12	**56**, 70	—
11	**48**	12	**57**, 27	**63**, 27
		24	—	**63**, 42

[a] Yields refer to isolated and purified products.
[b] This compound was obtained as an inseparable mixture of pyrazolidinone/pyrazolone (12:1).
[c] The same regioisomeric mixture was obtained in this case, however with a different pyrazolidinone/pyrazolone ratio (7:1).
[d] Yields were determined by NMR analysis.

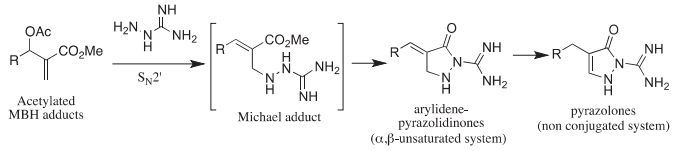
In this reaction, we observe net influence of the substituent attached to the aromatic ring into the ratio of products. Curiously after 12 h, in some acetylated adducts where the aromatic ring was substituted with an electron-withdrawing group, the pyrazolones were formed, as unique products in moderate yields (Table 4 entries 1 and 8).

However, when the aromatic ring was substituted by electron-donating groups or replaced by aliphatic substituents the arylidene pyrazolidinones were the only formed products, even after 48 h of reflux (Table 4, entries 3–7 and 9–10). Searching to change the product distribution toward the pyrazoles, we have increased the amount of triethylamine (from 3 to 20 equiv), however no change was observed.

The only exception was observed for **39** (Table 4, entry 2). In this particular case, after 12 h an arylidene pyrazolidinone was obtained as the only product. When the reaction was refluxed for 12 h more, however, **39** was completely converted to a pyrazolone in 56% yield (Table 4, entry 2).

Based on Table 4, thermodynamic control is likely and guided by the influence of the substituents attached to the aromatic ring. The pyrazolidinones are the sole products formed from the reaction between the acetylated adduct and amino-guanidine and we assume that the interconversion barriers between the pyrazolidinones and the pyrazolones are low.

If this hypothesis is correct, the presence of electron-donating groups or even the absence of substituents should contribute to stabilize much more the formation of pyrazolidinones than of pyrazolones, even after a long period of heating. But the presence of electron-withdrawing groups should destabilize the formation of pyrazolidinones, favoring pyrazolones (Scheme 2).



Scheme 2. Thermodynamic control as hypothesis to explain the pyrazolidinone/pyrazole ratio.

We decided therefore to compare the relative stability of our pyrazolidinones and pyrazolones via theoretical calculations at the B3LYP/cc-pVDZ level (Table 5). To our surprise, calculations revealed that the ΔE differences for all cases varied from 8.7 to 9.7 kcal mol^{-1} in favor of the pyrazolones. Most probably, this stability can be rationalized if the pyrazolone unity displays some aromatic character.

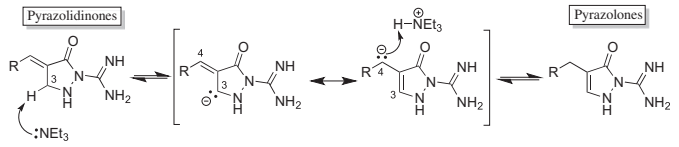
Table 5
Geometries and energies of theoretical and experimental compounds calculated at B3LYP/cc-pVDZ level

(R)	$E_{pyrazolidinone}$ (a.u.)	$E_{pyrazolone}$ (a.u)	ΔE (kcal mol^{-1})[a]
4-MeO	−832.7053991 (**53**)	−832.7193084[b]	8.7
H	−718.492495 (**55**)	−718.5074739[b]	9.4
4-NO_2	−922.5184813[b]	−922.5339952 (**58**)	9.7

[a] $\Delta E=(|E_{pyrazolidine}|-|E_{pyrazole}|)\cdot 627.5095$.
[b] These compounds are not part of this work, they are used only for calculations.

The data obtained from theoretical calculations failed to confirm the thermodynamic control hypothesis. Therefore, we moved our attention toward the interconversion barriers between the regioisomers. This interconversion should be mediated by basic catalysis, through the abstraction of the hydrogen at C3 to form a π-allyl system, which in turn is protonated at the benzylic position to generate the corresponding pyrazolone (Scheme 3).

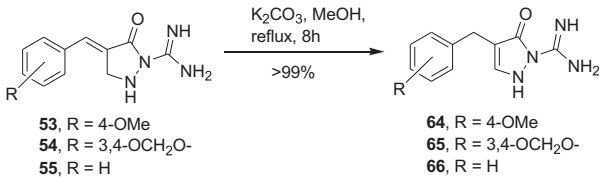
Apparently the acidity of the hydrogen at C3 is the determinant factor for the interconversion between the heterocycles. A new analysis of the data reported in Table 4 reveals that the acidity of hydrogen at C3 has a direct relationship with the nature of the substituents. That is, electron-withdrawing substituents increase



Scheme 3. Proposed mechanism for the base-mediated interconversion pyrazolidinones/pyrazolones.

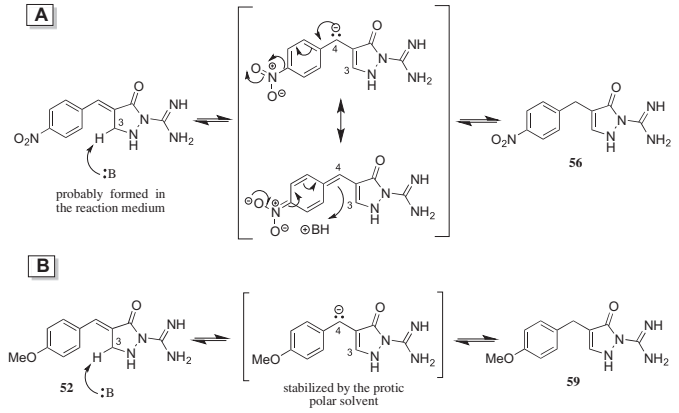
the relative acidity of the hydrogen at C3 leading to lower energy of activation for this abstraction.

Pyrazolidinones **53**, **54**, and **55** (Table 4) were also treated with K_2CO_3 in the presence of MeOH. This protocol has been used by Kim et al.[25] to form pyrimidines from MBH adducts, and seems appropriate since the pyrazolidinones are more soluble in MeOH than in CH_3CN. Indeed, all pyrazolidinones were quantitatively converted to the corresponding pyrazolones after 8 h of heating (Scheme 4). It is worth noting that we have treated the pyrazolidinone **55** with Et_3N in CH_3CN in order to obtain pyrazolone **66**, however after 72 h of reflux no double bond isomerization has been detected in the isolated product.



Scheme 4. Converting pyrazolidinones into pyrazolones.

As the basicity of triethylamine is comparable to that of K_2CO_3 (pK_b 3.67 against pK_b 3.29, respectively), these results indicate that the conjugate base of these compounds is more stabilized by a protic polar solvent as MeOH than by an aprotic polar solvent, such as CH_3CN. This stabilization should contribute to increase the acidity of C3-H, independently of the substituents attached to the aromatic ring. Based on these experimental observations, the selectivity of this reaction seems to be only governed by the interconversion barriers between pyrazolidinones and pyrazolones (Scheme 5).



Scheme 5. Stabilizing charges after deprotonation.

Canonic forms can help to explain the increasing of the hydrogen (C3) acidity when electron-withdrawing groups are present on the aromatic unity (Scheme 5, part A). The negative charge of the π-allylic system can be promptly stabilized by delocalization through the electron poor aromatic ring. This delocalization is more efficient when the substituents can act by resonance (*ortho*- or *para*-positions—Table 4, entries 1, 2, and 8). Electron-withdrawing groups acting by inductive effects are weaker and consequently less effective to stabilize the negative charge (Table 4, entries 3, 4, and 11). This stabilization became less likely when electron-donating substituents are present on the aromatic rings and is unfeasible without the presence of an aromatic ring. These difficulties can be however compensated by the presence of a polar protic solvent, which can probably stabilize the charge by solvation.

Curiously, when the reactions were performed in the presence of K_2CO_3 in MeOH we only observed the formation of a complex mixture of products.

3. Conclusions

Efficient and direct preparation of pyrazolidin-5-ones and pyrazol-5-ones from the reaction between silylated and acetylated MBH adducts with aminoguanidine is described. Diastereoselectivities varying from 2:1 to 7:1 were obtained when silylated adducts were treated with aminoguanidine. When acetylated adducts are used as substrate, arylidene pyrazolidin-5-ones are prepared in moderate to good yields.

The pyrazolidin-5-ones can be directly converted to pyrazol-5-ones with selectivity being related to the acidity of hydrogen attached to a carbon in a C–N σ bond. We have also demonstrated the favoring of polar aprotic solvents for this interconversion.

This seems to be the first report on the use of aminoguanidine as nucleophile in a Michael reaction with MBH adducts. The new heterocycles synthesized in this work are currently under biological evaluation and the results will be reported in due course.

4. Experimental section

4.1. General

The reaction progress was monitored by thin layer chromatography on silica gel (aluminum foils) and spotted under UV light (254 nm), followed by staining with ethanolic 25% phosphomolybdic solution or aqueous $KMnO_4$. Purifications were carried out by column chromatography on silica gel (70–230 or 230–400 mesh).^{1}H NMR spectra were recorded at 250 MHz, 500 MHz or 600 MHz and the ^{13}C NMR spectra at 62.5 MHz, 125 MHz or 150 MHz, in $CDCl_3$, MeOD or DMSO-d_6 at room temperature. Chemical shifts (δ) were reported in parts per million and the coupling constants (J) in Hertz (Hz). Signal multiplicity was assigned as singlet (s), doublet (d), double doublet (dd), triplet (t), double triplet (dt), multiplet (m) and broad (br). The high resolution mass spectra were recorded using a Q-TOF Micromass equipment (Waters, UK). Spectral data for known compounds (silylated and acetylated Morita–Baylis–Hillman adducts) are available in the Supplementary data. The compounds are named according to IUPAC rules using the program MarvinSketch version 5.9.3.

4.2. General procedure for the preparation of silylated pyrazolidin-5-ones

To a mixture of silylated MBH adduct (1.00 mmol) in methanol (20 mL) was added Et_3N (0.7 mL) and aminoguanidine bicarbonate (1.05 mmol). The resulting solution was stirred under reflux for 3 h. After, the solvent was removed and the crude residue was purified by silica gel flash chromatography ($CHCl_3$:MeOH) to afford **28**–**34** in 78–88% yield.

*4.2.1. 4-{[(tert-Butyldimethylsilyl)oxy](4-nitrophenyl)methyl}-5-oxopyrazolidine-1-carboximidamide (**28a/b**).* Yield: 83%; yellow tinged solid. ν_{max} (KBr) 3411, 2955, 1667, 1615 cm^{-1} δ_H (250 MHz, MeOD) (minor regioisomer) −0.03 (3H, s), 0.18 (3H, s), 0.98 (9H, s), 3.01–3.08 (1H, m), 3.47 (1H, dd, *J* 12.6, 5.6 Hz), 3.70 (1H, dd, *J* 12.5, 6.8 Hz), 5.44 (1H, d, *J* 5.0 Hz), 7.70 (2H, d, *J* 8.6 Hz, aromatics), 8.23 (2H, d, *J* 8.6 Hz, aromatics); (major regioisomer) −0.04 (3H, s), 0.16 (3H, s), 0.95 (9H, s), 2.82–2.90 (1H, m), 3.32 (1H, m), 3.78 (1H, dd, *J* 11.8, 10.4 Hz), 5.70 (1H, d, *J* 2.7 Hz), 7.71 (2H, d, *J* 8.6 Hz), 8.30 (2H, d, *J* 8.6 Hz); δ_C (62.5 MHz, MeOD) −4.9, −4.5, 19.2, 26.4, 26.6, 51.0, 52.3, 74.0, 124.1, 124.6, 128.6, 128.6, 148.9, 149.1, 149.9, 152.1, 162.6, 163.3, 178.4; HRMS (ESI): $[M+H]^+$, found 394.1934. $C_{17}H_{28}N_5O_4Si$ requires 394.1911.

*4.2.2. 4-{[(tert-Butyldimethylsilyl)oxy](2-fluorophenyl)methyl}-5-oxopyrazolidine-1-carboximidamide (**29a/b**).* Yield: 81%; white solid. ν_{max} (KBr) 3411, 2955, 1667, 1615 cm^{-1} δ_H (250 MHz, MeOD) −0.11 (3H, s), 0.10 (3H, s), 0.90 (9H, s), 2.80–2.88 (1H, m), 3.33–3.38 (1H, m), 3.79 (1H, dd, *J* 12.0, 9.4 Hz), 5.84 (1H, d, *J* 2.3 Hz), 7.03–7.11 (1H, m), 7.18–7.23 (1H, m), 7.28–7.35 (1H, m), 7.56 (1H, td, 7.4, 1.5 Hz); δ_C (62.5 MHz, MeOD) −4.8, −4.6, 19.2, 26.6, 49.4, 68.3, 116.4 (d, *J* 21.6 Hz), 125.2 (d, *J* 3.4 Hz), 129.7 (d, *J* 4.4 Hz), 130.4 (d, *J* 7.8 Hz), 131.2 (d, *J* 13.8 Hz), 1.60.5 (d, *J* 244.9 Hz), 163.2, 178.3; HRMS (ESI): $[M+H]^+$, found 367.1960. $C_{17}H_{27}FN_4O_2Si$ requires 394.1966.

*4.2.3. 4-{[(tert-Butyldimethylsilyl)oxy](3-chlorophenyl)methyl}-5-oxopyrazolidine-1-carboximidamide (**30a/b**).* Yield: 78%; white solid. ν_{max} (KBr) 3453, 2954, 1638, 1586, 1491 cm^{-1} δ_H (250 MHz, MeOD) −0.08 (3H, s), 0.11 (3H, s), 0.92 (9H, s), 2.75–2.83 (1H, m), 3.32 (1H, m), 3.76 (1H, dd, *J* 11.9, 9.5 Hz), 5.53 (1H, d, *J* 2.2 Hz), 7.31–7.37 (m, 3H), 7.45 (1H, s); δ_C (62.5 MHz, MeOD) −4.7, −4.6, 18.4, 26.2, 48.2, 49.6, 71.4, 124.8, 126, 127.3, 130.4, 133.3, 146.7, 162.1, 174.4; HRMS (ESI): $[M+H]^+$, found 383.1701. $C_{17}H_{27}ClN_4O_2Si$ requires 383.1670.

*4.2.4. 4-{[(tert-Butyldimethylsilyl)oxy](4-chlorophenyl)methyl}-5-oxopyrazolidine-1-carboximidamide (**31a/b**).* Yield: 88%; white solid. ν_{max} (KBr) 3454, 3325, 2954, 1641, 1590, 1494 cm^{-1} δ_H (250 MHz, MeOD) −0.12 (3H, s), 0.09 (3H, s), 0.90 (9H, s), 2.74 (1H, dt, *J* 8.2, 2.5 Hz), 3.33 (1H, m), 3.72 (1H, dd, *J* 12.1, 8.2 Hz), 5.48 (1H, d, *J* 2.7 Hz), 7.31–7.41 (4H, m); δ_C (62.5 MHz, MeOD) −4.6, −4.1, 17.6, 25, 49.7, 72.5, 127.4, 127.9, 132.7, 141.6, 161.6, 177.3; HRMS (ESI): $[M+H]^+$, found 383.1611. $C_{17}H_{27}ClN_4O_2Si$ requires 383.1670.

*4.2.5. 4-{[(tert-Butyldimethylsilyl)oxy](4-tert-butylphenyl)methyl}-5-oxopyrazolidine-1-carboximidamide (**32a/b**).* Yield: 83%; white solid. ν_{max} (KBr) 3454, 2956, 1663, 1610, 1485 cm^{-1} δ_H (250 MHz, MeOD) −0.12 (3H, s), 0.08 (3H, s), 0.90 (9H, s), 1.31 (9H, s), 2.70–2.90 (1H, m), 3.36–3.45 (1H, m), 3.59–3.80 (1H, m), 5.17 (1H, d, *J* 5.1 Hz, minor diastereoisomer), 5.50 (1H, d, *J* 2.2 Hz, major diastereoisomer), 7.29–7.41 (4H, m); δ_C (62.5 MHz, MeOD) −4.6, −4.4, 19.2, 26.5, 32, 35.5, 51.5, 52.6, 74.5, 126.3, 127.1, 141.2, 151.6, 163.1, 179.3; HRMS (ESI): $[M+H]^+$, found 405.2700. $C_{21}H_{37}N_4O_2Si$ requires 405.2686.

*4.2.6. 4-{[(tert-Butyldimethylsilyl)oxy](4-methoxyphenyl)methyl}-5-oxopyrazolidine-1-carboximidamide (**33a/b**).* Yield: 81%; white solid. ν_{max} (KBr) 3397, 2959, 1611, 1483 cm^{-1} δ_H (250 MHz, MeOD) −0.07 (3H, s), 0.12 (3H, s), 0.94 (9H, s), 2.73–2.80 (1H, m), 3.39–3.47 (1H, m), 3.76–3.81 (1H, m), 5.50 (1H, d, *J* 2.3 Hz), 6.92 (2H, d, *J* 8.5 Hz), 7.33 (2H, d, *J* 8.5 Hz); δ_C (62.5 MHz, MeOD) −4.3, −4.9, 17.3, 24.9, 47.5, 49.5, 54.3, 72, 112.9, 126.3, 134, 158.3, 160.7, 176.8; HRMS (ESI): $[M+H]^+$, found 379.2141. $C_{18}H_{30}N_4O_3Si$ requires 379.2165.

*4.2.7. 4-{2H-1,3-Benzodioxol-5-yl[(tert-butyldimethylsilyl)oxy]methyl}-5-oxopyrazolidine-1-carboximidamide (**34a/b**).* Yield: 83%; white solid. ν_{max} (KBr) 3345, 2954, 1664, 1487 cm^{-1} δ_H (250 MHz, MeOD) −0.07 (3H, s), 0.11 (3H, s), 0.92 (9H, s), 2.70–2.77 (1H, m), 3.33–3.41 (1H, m), 3.78 (1H, dd, *J* 12.0, 9.2 Hz), 5.46 (1H, d, *J* 2.4 Hz) 5.99 (2H, s), 6.78–6.92 (3H, m); δ_C (62.5 MHz, MeOD) −4.5, 18.4, 26.3, 48.2, 49.9, 71.8, 101.3, 106.6, 108.3, 119.1, 137.9, 146.4, 147.4, 161.7, 174.7; HRMS (ESI): $[M+H]^+$, found 393.1962. $C_{18}H_{29}N_4O_4Si$ requires 393.1958.

4.3. General procedure for the preparation of pyrazolidin-5-ones (49–57) and pyrazol-5-ones (58–63)

To a solution of the acetylated Morita–Baylis–Hillman adduct (1 mmol) in acetonitrile (30 mL) was added the guanidine carbonate (0.83 mmol) and triethylamine (5 mmol). The resulting yellow suspension was stirred, under reflux, for 12 h. After this time a precipitate is formed. The reaction was cooled to room temperature the reaction was filtered and the filtrate was washed successively with acetonitrile to provide the corresponding pyrazolidin-5-ones and pyrazol-5-ones.

*4.3.1. (4E)-4-[(2-Fluorophenyl)methylidene]-5-oxopyrazolidine-1-carboximidamide (**49**).* Yield: 30%; yellow tinged solid; mp 227–229 °C; ν_{max} (KBr) 3404, 3294, 3207, 3065, 1682, 1588, 1482, 1452, 1360, 1305, 1224 cm^{-1} δ_H (250 MHz, DMSO-d_6) 4.39 (2H, d, *J* 0.5 Hz), 4.82 (2H, s), 6.76 (2H, br s), 7.24–7.48 (5H, m); δ_C (62.5 MHz, DMSO-d_6) 52.5, 52.5, 115.5, 115.8, 112.7, 123, 123.7, 123.7, 124.5, 124.5, 130.4, 130.5, 130.7, 157.9, 161.2, 161.8, 168.4; HRMS (ESI): $[M+H]^+$, found 235.1004. $C_{11}H_{11}FN_4O$ requires 235.0995.

*4.3.2. (4E)-4-[(3-Chlorophenyl)methylidene]-5-oxopyrazolidine-1-carboximidamide (**50**).* Yield: 58%; yellow tinged solid; ν_{max} (KBr) 3417, 3291, 1661, 1573, 1484, 1414, 1372, 727 cm^{-1} δ_H (250 MHz, DMSO-d_6) (major regioisomer) 4.51 (2H, d, *J* 2.5 Hz), 4.85 (2H, s), 6.76 (2H, br s), 7.23–7.43 (5H, m); δ_C (62.5 MHz, DMSO-d_6) (major regioisomer) 52.5 (d, *J* 2.8 Hz), 115.7 (d, *J* 21.4 Hz), 122.8 (d, *J* 13.8 Hz), 123.7 (d, *J* 3.7 Hz), 124.5 (d, *J* 3.3 Hz), 130.4 (d, *J* 2.4 Hz), 130.5, 130.7, 159.8 (d, *J* 247.0 Hz), 161.2, 168.4; HRMS (ESI): $[M+H]^+$, found 251.0718. $C_{11}H_{11}ClN_4O$ requires 251.0700.

*4.3.3. (4E)-4-[(4-Chlorophenyl)methylidene]-5-oxopyrazolidine-1-carboximidamide (**51**).* Yield: 66%; yellow tinged solid; ν_{max} (KBr) 3397, 1691, 1638, 1585, 1492, 1366, 1097, 816 cm^{-1} δ_H (250 MHz, DMSO-d_6) (major regioisomer) 4.50 (2H, d, *J* 2.5 Hz), 4.83 (2H, s), 6.76 (2H, br s), 7.34–7.38 (3H, m), 7.50 (2H, d, *J* 8.5 Hz); δ_C (62.5 MHz, DMSO-d_6) (mixture of regioisomers) 32.7, 52.6, 116.9, 128, 128.6, 128.9, 130.1, 130.4, 130.5, 131.2, 132.9, 134.1, 139.5, 141.4, 156.2, 161, 168.5, 169.1; HRMS (ESI): $[M+H]^+$, found 251.0602. $C_{11}H_{11}ClN_4O$ requires 251.0700.

*4.3.4. (4E)-4-[(4-tert-Butylphenyl)methylidene]-5-oxopyrazolidine-1-carboximidamide (**52**).* Yield: 45%; yellow tinged solid; mp 210–211.8 °C; ν_{max} (KBr) 3394, 2959, 1678, 1589, 1493, 1357, 1308, 566 cm^{-1} δ_H (250 MHz, DMSO-d_6) 1.31 (9H, s), 4.52 (2H, d, *J* 2.5 Hz), 4.83 (2H, s), 6.73 (2H, br s), 7.27 (2H, d, *J* 8.5 Hz), 7.39 (1H, s), 7.47 (2H, d, *J* 8.3 Hz); δ_C (62.5 MHz, DMSO-d_6) 31, 34.4, 52.8, 125.4, 127.5, 129.4, 131.2, 132.4, 151, 160.9, 168.9; HRMS (ESI): $[M+H]^+$, found 273.1698. $C_{15}H_{20}N_4O$ requires 273.1715.

*4.3.5. (4E)-4-[(4-Methoxyphenyl)methylidene]-5-oxopyrazolidine-1-carboximidamide (**53**).* Yield: 65%; yellow tinged solid; mp 214.2–215.4 °C; ν_{max} (KBr) 3465, 3179, 3087, 3046, 1658, 1646, 1608, 1570, 1548, 1456, 1359, 1230 cm^{-1} δ_H (250 MHz, DMSO-d_6) 3.81 (3H, s), 4.51 (2H, d, J 2.4 Hz), 4.83 (2H, s), 6.71 (2H, br s), 7.02 (2H, d, *J* 8.7 Hz), 7.39 (2H, d, *J* 9.2 Hz), 7.37 (1H, t, *J* 2.4 Hz); δ_C (62.5 MHz,

DMSO-d_6) 53, 55.3, 114.1, 126, 127.7, 131.2, 131.2, 159.3, 160.9, 169; HRMS (ESI): $[M+H]^+$, found 247.1209. $C_{12}H_{14}N_4O_2$ requires 247.1195.

*4.3.6. (4E)-4-(2H-1,3-Benzodioxol-5-ylmethylidene)-5-oxopyrazolidine-1-carboximidamide (**54**).* Yield: 76% (after 12 h) and 86% (after 48 h); yellow tinged solid; mp 234–235.7 °C; ν_{max} (KBr) 3433, 3314, 3014, 1657, 1642, 1578, 1504, 1488, 1341 cm^{-1} δ_H (250 MHz, DMSO-d_6) (data for the hydrochloride) 4.79 (2H, s), 5.41 (2H, s), 6.13 (2H, s), 7.07 (3H, m), 7.68 (1H, s), 8.46 (2H, s), 11.66 (1H, br s); δ_C (62.5 MHz, DMSO-d_6) 52.2, 101.9, 108.8, 110, 119.2, 126.4, 127.4, 138.5, 147.9, 149.1, 153.4, 160.4; HRMS (ESI): $[M+H]^+$, found 261.0980. $C_{12}H_{13}N_4O_3$ requires 261.0988.

*4.3.7. (4E)-5-Oxo-4-(phenylmethylidene)pyrazolidine-1-carboximidamide (**55**).* Yield: 65%; yellow tinged solid; mp 205–207.5 °C; ν_{max} (KBr) 3398, 3294, 3209, 3165, 3056, 1681, 1626, 1584, 1490, 1370, 770 cm^{-1} δ_H (250 MHz, DMSO-d_6) 4.52 (2H, d, *J* 2.6 Hz), 4.87 (2H, s), 6.67 (1H, br s), 7.06 (2H, br s), 7.32–7.40 (4H, m), 7.46 (2H, t, *J* 7.5 Hz); δ_C (62.5 MHz, DMSO-d_6) 52.8, 128.2, 128.3, 128.6, 129.5, 131.4, 135.2, 161, 168.7; HRMS (ESI): $[M+H]^+$, found 217.1039. $C_{12}H_{14}N_4O_2$ requires 271.1089.

*4.3.8. (4E)-4-(Cyclohexylmethylidene)-5-oxopyrazolidine-1-carboximidamide (**56**).* Yield: 70%; white solid; mp 215–216.5 °C; ν_{max} (KBr) 3436, 3273, 2921, 2850, 1660, 1635, 1583, 1477, 1377 cm^{-1} δ_H (250 MHz, DMSO-d_6) 1.17–1.37 (5H, m), 1.57–1.72 (5H, m), 2.05–2.17 (1H, m), 4.20 (2H, d, J 2.5 Hz), 4.78 (2H br s), 6.26 (1H, dd, J 7.5, 2.5 Hz); δ_C (62.5 MHz, DMSO-d_6) 25.6, 25.8, 31.9, 36.6, 51.6, 125.9, 140, 161.5, 169; HRMS (ESI): $[M+H]^+$, found 223.1580. $C_{11}H_{19}N_4O$ requires 223.1559.

*4.3.9. (4E)-4-[(3-Nitrophenyl)methylidene]-5-oxopyrazolidine-1-carboximidamide (**57**).* Yield: 27%; yellow solid. δ_H (250 MHz, DMSO-d_6, mixture of regioisomers) 3.61 (2H, s), 4.56 (2H, s). 4.89 (2H, s), 5.73 (2H, s), 6.79–7.10 (4H, m), 7.50 (1H, s), 7.49–7.59 (2H, m), 7.73–7.82 (3H, m), 8.12 (4H, m); δ_C (62.5 MHz, DMSO-d_6) 32.6, 52.4, 116, 120.9, 122.8, 123, 123.4, 129, 129.4, 130.1, 130.7, 135.6, 135.9, 136.9, 141.9, 143.2, 147.6, 147.9, 156.3, 160.9, 168.1, 169.1; HRMS (ESI): $[M+H]^+$, found 262.0933. $C_{11}H_{11}N_5O_3$ requires 262.0940.

*4.3.10. 4-[(4-Nitrophenyl)methyl]-5-oxo-2,5-dihydro-1H-pyrazole-1-carboximidamide (**58**).* Yield: 53%; yellowish solid; mp 263–265 °C; ν_{max} (KBr) 3422, 3350, 3281, 3072, 1679, 1651, 1584, 1511, 1457, 1346, 1110 cm^{-1} δ_H (250 MHz, DMSO-d_6) 3.62 (2H, s), 5.68 (2H, s). 6.66 (2H, s), 7.22 (1H, s), 7.72 (2H, d, *J* 8.5 Hz), 8.12 (2H, d, *J* 8.8 Hz); δ_C (62.5 MHz, DMSO-d_6) 32.8, 115.8, 123.2, 129.7, 142, 145.8, 149.2, 156.3, 169.1; HRMS (ESI): $[M+H]^+$, found 262.0971. $C_{11}H_{11}N_5O_3$ requires 262.0940.

*4.3.11. 4-[(2-Fluorophenyl)methyl]-5-oxo-2,5-dihydro-1H-pyrazole-1-carboximidamide (**59**).* Yield: 53%; yellowish solid; mp 250.8–251.5 °C; ν_{max} (KBr) 3427, 3292, 3204, 3083, 1682, 1651, 1613, 1591, 1515, 1488, 1227 cm^{-1} δ_H (250 MHz, DMSO-d_6) 3.48 (2H, s), 5.70 (2H, s), 6.75 (2H, s), 6.87 (1H, s), 7.08–7.22 (4H, m); δ_C (62.5 MHz, DMSO-d_6) 26.0 (d, *J* 3.2 Hz), 115.0 (d, *J* 21.9 Hz), 115.6, 124.1 (d, *J* 3.3 Hz), 126.5 (d, *J* 15.6 Hz), 128.0 (d, *J* 7.9 Hz), 131.2 (d, *J* 4.6 Hz), 141.1, 156.1, 160.4 (d, *J* 243.5 Hz); 169.0; HRMS (ESI): $[M+H]^+$, found 235.0987. $C_{11}H_{11}FN_4O$ requires 235.0995.

*4.3.12. 4-[(4-Methanesulfonylphenyl)methyl]-5-oxo-2,5-dihydro-1H-pyrazole-1-carboximidamide (**62**).* Yield: 59%; yellowish solid; mp 250.5–252.5 °C; ν_{max} (KBr) 3421, 3348, 3017, 2912, 1673, 1638, 1593, 1501, 1463, 1298, 1148 cm^{-1} δ_H (250 MHz, DMSO-d_6) 3.15 (3H, s), 3.59 (2H, s), 5.67 (2H, s), 6.63 (2H, s), 7.18 (1H, s), 7.51 (2H, d, *J* 8.3 Hz), 7.81 (2H, d, *J* 8.3 Hz); δ_C (62.5 MHz, DMSO-d_6) 32.9, 43.7, 116.1, 126.8, 129.5, 138.4, 141.9, 147, 156.3, 169.2; HRMS (ESI): $[M+H]^+$, found 295.0889. $C_{12}H_{14}N_4O_3S$ requires 295.0865.

*4.3.13. 4-[(3-Nitrophenyl)methyl]-5-oxo-2,5-dihydro-1H-pyrazole-1-carboximidamide (**63**).* Yield: 42%; yellowish solid; mp 240.6–242.9 °C; ν_{max} (KBr) 3334, 3092, 1673, 1520, 1455, 1344, 819, 736, 668 cm^{-1} δ_H (250 MHz, DMSO-d_6) 3.61 (2H, s), 5.73 (2H, s), 6.81 (2H, brs), 7.30 (1H, s), 7.56 (1H, t, *J* 7.8 Hz), 7.74 (1H, d, *J* 7.5 Hz), 8.04 (1H, d, *J* 6.9 and 8.0 Hz), 8.11 (1H, s); δ_C (62.5 MHz, DMSO-d_6) 32.7, 116.2, 121.3, 123.4, 129.7, 135.9, 143.1, 148.1, 156.7, 169.7, 169.8; HRMS (ESI): $[M+H]^+$, found 262.0933. $C_{12}H_{14}N_4O_3S$ requires 262.0940.

4.4. General procedure for the isomerization of pyrazolidin-5-ones 53, 54, and 55 to pyrazol-5-ones 64, 65, and 66

To a suspension of 52 or 54 (0.5 mmol) in methanol (10 mL) was added K_2CO_3 (1.0 mmol). The resulting mixture was stirred under reflux for 8 h. After this period we observed the complete dissolution of the reagents into the solvent. Then, the solvent was removed under reduced pressure and the residue was washed with distilled water (2×5 mL) and dried under vacuum to provide the pyrazol-5-ones as unique products.

*4.4.1. 4-[(4-Methoxyphenyl)methyl]-5-oxo-2,5-dihydro-1H-pyrazole-1-carboximidamide (**64**).* Yield: >99%; white solid; mp 205.5–207.5 °C. ν_{max} (KBr) 3420, 3295, 1679, 1648 cm^{-1} δ_H (500 MHz, DMSO-d_6) 3.38 (2H, s), 3.71 (3H, s), 5.69 (2H, s), 6.72 (2H, br s), 6.83 (2H, d, *J* 8.6 Hz), 6.90 (2H, s), 7.14 (2H, d, *J* 8.6 Hz); δ_C (62.5 MHz, DMSO-d_6) 32.1, 55, 113.6, 117.9, 129.8, 132, 140.9 156, 157.5, 169.3; HRMS (ESI): $[M+H]^+$, found 247.1215. $C_{12}H_{14}N_4O_2$ requires 247.1195.

*4.4.2. 4-(2H-1,3-Benzodioxol-5-ylmethyl)-5-oxo-2,5-dihydro-1H-pyrazole-1-carboximidamide (**65**).* Yield: >99%; white solid. ν_{max} (KBr) 3431, 3299, 1682, 1649 cm^{-1} δ_H (250 MHz, DMSO-d_6) 3.38 (2H, s), 5.75 (2H, s), 5.94 (2H, s), 6.68–6.71 (1H, m), 6.78–6.81 (1H, m), 6.90 (2H, s), 6.93 (1H, br s), 7.03 (1H, s); δ_C (62.5 MHz, DMSO-d_6) 32.5, 100.6, 107.9, 109.2, 117.5, 117.9, 121.6, 133.9, 141.4, 145.3, 147, 155.9, 168.9; HRMS (ESI): $[M+H]^+$, found 261.0979. $C_{12}H_{14}N_4O_2$ requires 261.0982.

*4.4.3. 4-Benzyl-5-oxo-2,5-dihydro-1H-pyrazole-1-carboximidamide (**66**).* Yield: >99%; white solid; mp 230.9–231.2 °C. ν_{max} (KBr) 3425, 3295, 1679, 1650, 1613, 1590, 1508, 1475 cm^{-1} δ_H (600 MHz, DMSO-d_6) 3.46 (2H, s), 5.71 (2H, s), 6.75 (2H, br s), 6.98 (1H, s), 7.16–7.19 (1H, m), 7.21–7.28 (4H, m); δ_C (150 MHz, DMSO-d_6) 33.4, 117.8, 126.3, 128.6, 129.2, 140.8, 141.6, 156.6, 169.7; HRMS (ESI): $[M+H]^+$, found 217.1081. $C_{11}H_{13}N_4O$ requires 217.1089.

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Supplementary data

Supplementary data with all spectroscopic data of pyrazolidin-5-ones and pyrazol-5-ones are available. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2012.10.057.

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