

Serendipity at work: unexpected ring transformations of 4-aminopyrazolidin-3-ones into *N*-aminohydantoins

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Dedicated to Professor Heinz Heimgartner, University of Zürich, on the occasion of his 70th anniversary

Abstract

Catalytic hydrogenation of (4*R**,5*R**)-4-benzyloxycarbonylamino-5-phenylpyrazolidin-3-one **2** in the presence of Pd-C furnished an unexpected 'ring switching' transformation product, 3-amino-5-benzylimidazolidine-2,4-dione **4**. Furthermore, heating of azomethine imines **3a,b** (derived from **2** and aromatic aldehydes) afforded the corresponding (*Z*)-5-benzylidene-3-[(*E*)-benzylideneamino]imidazolidine-2,4-diones **8a,b** as ring transformation products. Both reactions are explainable by cleavage of the C(5)–N(1) single bond in substrates **2** and **3** followed by cyclocondensation of the amide nitrogen to the carbamate carbonyl group. The structure of hydantoin **8a** was confirmed by X-ray diffraction.

Keywords: Pyrazolidin-3-ones, azomethine imines, ring transformations, hydantoins

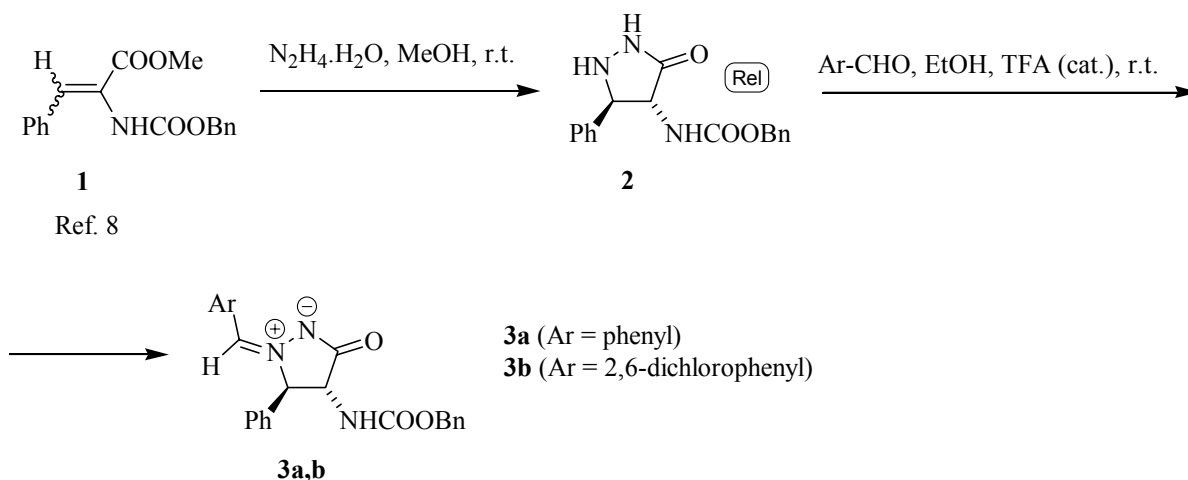
Introduction

The importance of pyrazolidin-3-ones has increased significantly in the last decades, due to their applicability in industrial processes, and because several pyrazolidin-3-one derivatives exhibit biological activities.¹ Recently, pyrazolidin-3-ones have also been employed as templates in enantioselective Diels-Alder² and Michael reactions.³ An important group of fused pyrazolidinone analogues are 2-acylamino-1-oxo-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-7-carboxylates (3-amino-1,5-diazabicyclo[3.3.0]octan-2-ones), which are useful scaffolds for the preparation of conformationally constrained peptide mimetics, such as Eli-Lilly's pyrazolo[1,2-*a*]pyrazolone based γ -lactam antibiotics LY 186826, LY 193239, and LY 255262.⁴

In the last decade, a substantial part of our research interest has also been devoted to the chemistry of pyrazolidinones with focus on 1,3-dipolar cycloadditions of (1*Z*,4*R**,5*R**)-1-benzylidene-3-oxotetrahydropyrazol-1-ium-2-ides (1-benzylidene-3-oxopyrazolidin-1-azomethine imines) to various dipolarophiles⁵ including combinatorial⁶ and ‘click’-cycloadditions.⁷ Generally, these cycloadditions were highly selective with quite predictable stereo-control tunable by the structure of the dipole and the dipolarophile.⁵⁻⁷ In continuation, we aimed at development of diversity-oriented synthesis of polysubstituted 6-acylamino-7-oxoperhydropyrazolo[1,2-*a*]pyrazole-1(or 2)-carboxylates with selectively deprotectable amino and carboxy function as useful scaffolds for the preparation of peptidomimetics. Within this context, *Z*-protected 2,3-dehydro-3-phenylalanine ester **1**⁸ was transformed into (4*R**,5*R**)-4-benzyloxycarbonylamino-5-phenylpyrazolidin-3-one **2** and its azomethine imine derivatives **3a,b** as the key-intermediates for further [3+2] cycloadditions leading to the desired scaffolds. However, two unexpected transformations were observed in the beginning of this study. First, attempted deprotection of **2** by catalytic hydrogenation afforded 3-amino-5-benzylhydantoin **4** instead of the corresponding free amine **5**. Second, cycloadditions of dipoles **3a,b** to *tert*-butyl acrylate in refluxing anisole afforded mixtures of isomeric cycloadducts and 5-benzylidene-3-(benzylideneamino)hydantoins **8a,b** as side products. Therefore, we decided to take a closer look at these reactions. Herein, we report these unusual and, to the best of our knowledge, so far unknown ring transformations of 4-aminopyrazolidin-3-ones into *N*-aminohydantoins.

Results and Discussion

Methyl 2-benzyloxycarbonylamino-3-phenylacrylate **1** was prepared from benzaldehyde and methyl 2-benzyloxycarbonylamino-2-(dimethoxyphosphoryl)acetate following the literature procedure.⁸ Further treatment of **1** with excess hydrazine hydrate in methanol at r.t. gave the pyrazolidinone **2** in 85% yield. Acid-catalyzed treatment of **2** with benzaldehyde and 2,6-dichlorobenzaldehyde gave the corresponding azomethine imines **3a** and **3b** in 81% and 73% yield, respectively (Scheme 1).



Scheme 1

The structures of the pyrazolidinone **2** and azomethine imines **3a** and **3b** were determined by NMR. First, the ($4R^*$, $5R^*$)-configuration of **2** was established on the basis of vicinal coupling constant, $^3J_{\text{H4-H5}}$. The coupling constant, $^3J_{\text{H4-H5}} = 11.1$ Hz, fitted within the typical order of magnitude, $^3J_{\text{H4-H5}} \sim 10\text{--}12$ Hz, measured previously in closely related 3-pyrazolidinones^{5,9} with the *trans*-configuration around the C(4)–C(5) bond. The structures of dipoles **3a,b** were determined by NOESY spectroscopy. NOE between the 1'-H and 5-H and NOE between 5-H and NH in compounds **3a** and **3b** were in agreement with the (*Z*)-configuration around the exocyclic C=N double bond and *trans*-configuration around the C(4)–C(5) bond. Other characteristic NMR data of compounds **3a,b** were also in agreement with the data for closely related dipoles (Figure 1).^{1,5,9,10}

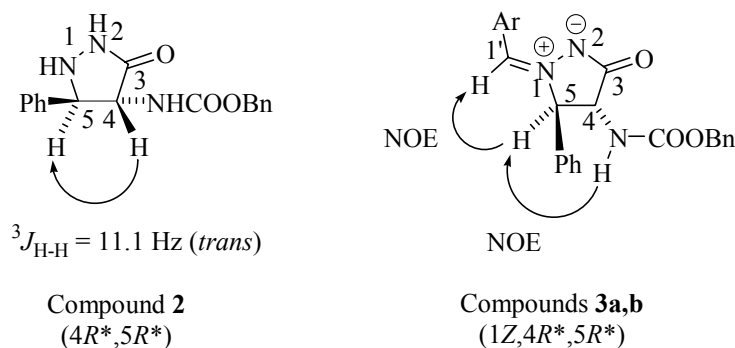
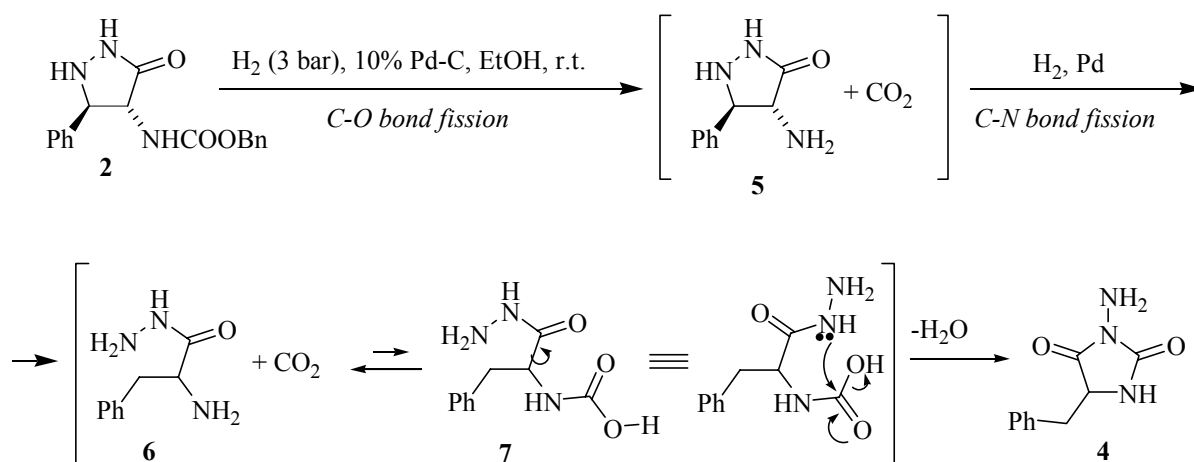


Figure 1

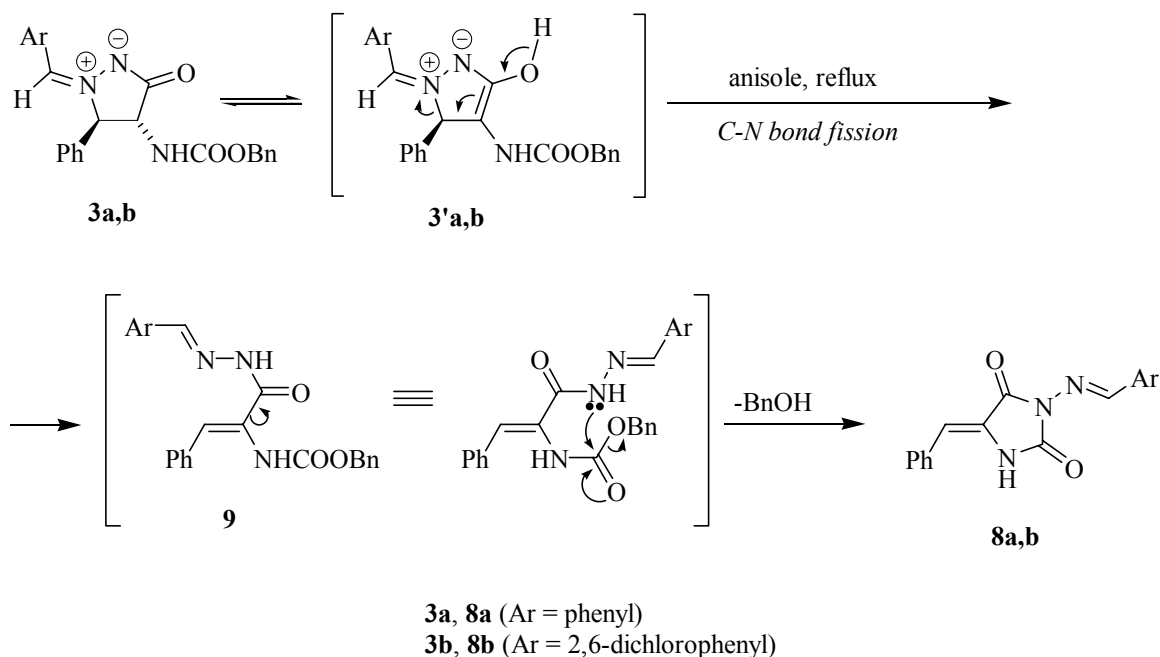
In order to prepare the unprotected ($4R^*$, $5R^*$)-4-amino-5-phenyl-3-pyrazolidinone **5**, compound **2** was catalytically hydrogenated under 3 bar of H_2 in ethanol in the presence of 10% Pd-C. The conversion was surprisingly slow and required 30 hours to completion. To our surprise, the isolated product was 3-amino-5-benzylimidazolidine-2,4-dione **4** and not the

expected compound **5**. A possible explanation for the formation of hydantoin **4** could be the following. Catalytic hydrogenation of benzyl carbamate **2** produces the amine **5** and CO₂ as the primary products. Next, hydrogenolytic cleavage of the benzylic C(5)–N(1) bond in **5** gives the open-chain intermediate **6**. Under slightly elevated pressure (3 bar), the amine **6** and CO₂ are in equilibrium with the carbamic acid **7**, which cyclizes into *N*-amino hydantoin **4**. The proposed mechanism is supported by known, closely related examples of cyclisations of *N*-benzyloxycarbonyl- α -amino acid hydrazides¹¹ and α -semicarbazidoacetates¹² into 3-aminoimidazolidine-2,4-diones. Besides, the above transformation is also related to Bucherer's synthesis of hydantoin, which proceeds in a closed vessel under slightly elevated pressure utilizing CO₂ (or carbonate) as a C₁-synthon (Scheme 2).¹³



Scheme 2

Finally, heating of azomethine imines **3a** and **3b** in anisole produced 3-benzylideneimino-5-benzylideneimidazolidine-2,4-diones **8a** and **8b** in 83% and 82% yield, respectively. Also here, the observed ring transformation is feasible only by cleavage of the C(5)–N(1) bond. Thus, a plausible rationale for this reaction includes rearrangement of heterocyclic enol **3'** to give the open-chain α,β -unsaturated hydrazide **9**, followed by intramolecular cyclocondensation to the benzyl carbamate residue to furnish the title compound **8** (Scheme 3). It is noteworthy, that the synthesis of compound **8a** and some of its close analogues by condensation of 5-unsubstituted 3-(benzylideneamino)hydantoin with aromatic aldehydes has already been reported previously.¹⁴



Scheme 3

The structures of novel compounds **2**, **3a**, **3b**, and **8b** and known compounds **4** and **8a** were determined by spectroscopic methods (IR, ^1H and ^{13}C NMR, NOESY spectroscopy, and MS) and by elemental analyses for C, H, and N. Compounds **2**, **3a**, and **3b** were not obtained in analytically pure form. Their identities were confirmed by ^{13}C NMR and/or EI-HRMS.

Physical and spectral data for known compound **4** were in agreement with the literature data.^{11a,12c} On the other hand, physical and spectral data for **8a** were not consistent with the literature data (see also Experimental).¹⁴ However, spectral data of **8a** were in agreement with the literature data for closely related 5-alkylidenehydantoin.¹⁵ Finally, the structure of compound **8a** was unambiguously determined by X-ray diffraction (Figure 2).

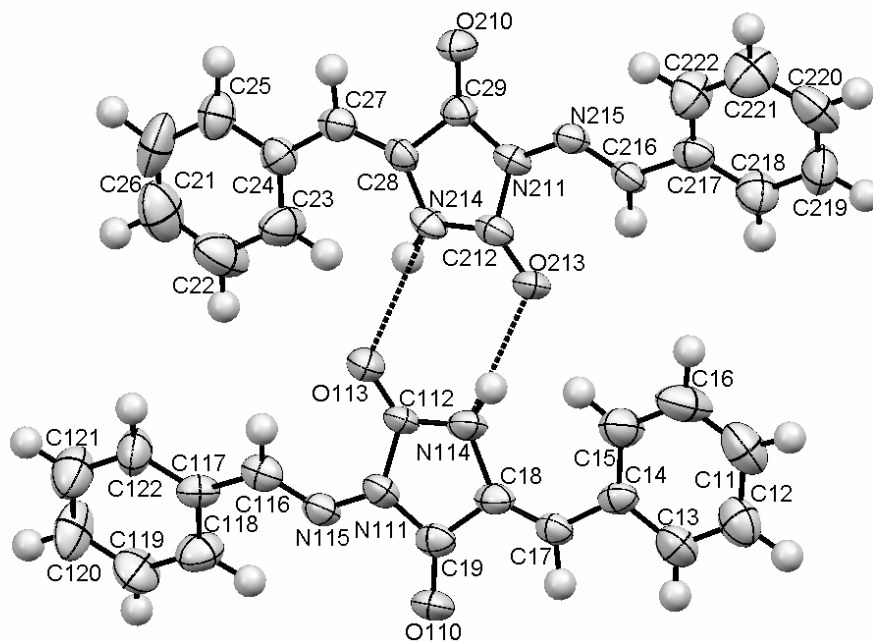


Figure 2. ORTEP plot of the dimeric unit of **8a** in the crystal structure. Ellipsoids are plotted at 50% probability, hydrogen bonds are depicted as dashed lines, and atom labeling of one asymmetric unit is shown.

Conclusions

Quite surprisingly and in contrast to their close *N*-benzoylated analogues,⁵⁻¹⁰ (4*R**,5*R**)-4-benzyloxycarbonylamino-5-phenylpyrazolidin-3-one **2** and its azomethine imine derivatives **3** undergo ‘ring switching’ transformations into 3-aminoimidazolidine-2,4-diones **4** and **8**, respectively. To the best of our knowledge, these are the first examples of such ring transformation (*i.e.* 4-acylaminopyrazolidin-3-one → 3-aminoimidazolidin-2,4-dione), which indicate that C(5)–N(1) bond in compounds **2** and **3** is particularly weak and, hence, easily cleaved under hydrogenolytic or thermal conditions. Weakness of C(5)–N(1) bond could be due to its benzyl-type bond character and due to the five-membered ring strain. Further transformations with various 5-substituted analogues of **2** and **3** shall be performed to elucidate the contribution of each factor to the C–N bond fission. At the moment, these ring transformations might not seem synthetically useful, since 5-substituted 3-aminohydantoin are easily available from *N*-protected α -amino acid hydrazides.^{11,12,14} However, it should be taken into account, that 4-acylaminopyrazolidin-3-ones as cyclic α -amino acid hydrazides are also easily available starting materials for a simple one-step synthesis of 3-aminoimidazolidin-2,4-diones.

Experimental Section

General. Melting points were measured on a Stanford Research Systems MPA100 OptiMelt automated melting point system. IR spectra were recorded on a Perkin-Elmer Spectrum BX FTIR spectrometer. ^1H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz, respectively, on a Bruker Avance DPX 300 instrument with DMSO- d_6 and CDCl_3 as solvents and TMS as internal standard. Mass spectra were recorded on an AutoSpecQ spectrometer. Elemental analyses for C, H, and N were obtained using Perkin-Elmer CHN Analyzer 2400 II. Catalytic hydrogenation was performed on a Parr Hydrogenation Apparatus 500 ml 3916EF. Column chromatography (CC) was performed on silica gel (Fluka, Silica gel 60, particle size: 0.035-0.070 mm).

Anisole, benzaldehyde, 2,6-dichlorobenzaldehyde, hydrazine hydrate, and 10% palladium on charcoal were purchased from Sigma-Aldrich and used without further purification. Methyl 2-(benzyloxycarbonylamino)-3-phenylacrylate **1** was prepared following the literature procedure.⁸

(4*R,5*R**)-4-Benzyloxycarbonylamino-5-phenylpyrazolidin-3-one (2).** A mixture of **1** (3.113 g, 10 mmol), methanol (15 mL), and hydrazine hydrate (2.50 mL, 50 mmol) was stirred at r.t. for 2 h. Then, water (35 mL) was added and stirring at r.t. was continued for 1 h. The precipitate was collected by filtration and washed with water (2×10 mL). White solid, yield 85%, 2.646 g, mp 165–170 °C, R_f (EtOAc) 0.30, IR (ν_{max} , cm^{-1}): 3418, 3351, 3235, 1717 (C=O), 1697 (C=O), 1538, 1290, 1243, 1056, 752, 697. ^1H NMR (300 MHz, DMSO- d_6), δ_{H} 4.34 (1H, t, $^3J_{\text{HH}} = 11.1$ Hz, 5-H), 4.36 (1H, dd, $^3J_{\text{HH}} = 8.9, 11.1$ Hz, 4-H), 5.01 (2H, s, CH_2Ph), 5.37 (1H, d, $^3J_{\text{HH}} = 11.1$ Hz, 1-H), 7.24–7.48 (10H, m, 2×Ph), 7.68 (1H, d, $^3J_{\text{HH}} = 8.9$ Hz, NHCOOBn), 9.47 (1H, s, 2-H). ^{13}C NMR (75.5 MHz, DMSO- d_6), δ_{C} 57.7, 65.6, 65.9, 127.4, 127.7, 127.8, 128.0, 128.3, 128.5, 156.2, 136.9, 140.0, 172.9. MS, $m/z = 312$ (MH^+), HRMS (ESI), $m/z = 312.1335$ (MH^+), $\text{C}_{17}\text{H}_{18}\text{N}_3\text{O}_3$ requires 312.1348. Anal. Calcd for $\text{C}_{17}\text{H}_{17}\text{N}_3\text{O}_3 \cdot \frac{1}{8}\text{H}_2\text{O}$ (313.59): C, 65.11; H, 5.54; N, 13.40%. Found: C, 65.13; H, 5.45; N, 13.55%.

General procedure for the preparation of azomethine imines (3a,b)

A mixture of **2** (1.557 g, 5 mmol), aromatic aldehyde (6 mmol), and ethanol (20 mL) was stirred at r.t. for 5 min. Then, trifluoroacetic acid (10 drops) was added and stirring at r.t. was continued for 3 h. The precipitate was collected by filtration and washed with ethanol (5 mL) and ether (2×5 mL).

(1*Z*,4*R,5*R**)-1-Benzylidene-4-benzyloxycarbonylamino-5-phenylpyrazolidin-1-ium-2-ide (3a).** Prepared from **2** (1.557 g, 5 mmol) and benzaldehyde (0.60 mL, 0.636 g, 6 mmol). White solid, yield 81%, 1.618 g, mp 202–207 °C, R_f (EtOAc) 0.35, IR (ν_{max} , cm^{-1}): 3433, 3189, 3034, 2988, 1721 (C=O), 1713 (C=O), 1654, 1591, 1568, 1454, 1351, 1321, 1252, 1155, 1070, 1040, 986, 916, 868, 757, 738, 685. ^1H NMR (300 MHz, DMSO- d_6), δ_{H} 4.30 (1H, dd, $^3J_{\text{HH}} = 5.5, 8.0$ Hz, 4-H), 5.04 (2H, s, CH_2Ph), 5.66 (1H, br d, $^3J_{\text{HH}} = 5.5$ Hz, 5-H), 7.26–7.39 (5H, m, Ph), 7.33

(1H, br s, 1'-H), 7.41–7.49 (5H, m, Ph), 7.49–7.57 (3H, m, 3H of Ph), 8.05 (1H, d, $^3J_{\text{HH}} = 7.6$ Hz, NHCOOBn), 8.27–8.35 (2H, m, 2H of Ph). ^{13}C NMR (75.5 MHz, DMSO- d_6), δ_{C} 59.7, 65.8, 77.0, 127.2, 127.8, 127.9, 128.4, 128.7, 129.2, 129.4, 131.5, 131.9, 134.3, 136.7, 137.3, 156.0, 159.0, 179.4. MS, $m/z = 400$ (MH^+), HRMS (ESI), $m/z = 400.1653$ (MH^+), $\text{C}_{24}\text{H}_{22}\text{N}_3\text{O}_3$ requires 400.1661. Anal. Calcd for $\text{C}_{24}\text{H}_{21}\text{N}_3\text{O}_3 \cdot \frac{1}{3}\text{H}_2\text{O}$ (405.45): C, 71.10; H, 5.39; N, 10.36%. Found: C, 71.07; H, 5.21; N, 10.58%.

(1Z,4R*,5R*)-4-Benzoyloxycarbonylamino-1-(2,6-dichlorobenzylidene)-5-phenylpyrazolidin-1-ium-2-ide (3b). Prepared from **2** (1.557 g, 5 mmol) and 2,6-dichlorobenzaldehyde (1.050 g, 6 mmol). White solid, yield 73%, 1.709 g, mp 202–210 °C, R_{f} (EtOAc) 0.30, IR (ν_{max} , cm^{-1}): 3458, 3415, 3269, 3061, 1707 (C=O), 1694 (C=O), 1609, 1523, 1434, 1314, 1280, 1108, 1093, 965, 775, 731, 698. ^1H NMR (300 MHz, DMSO- d_6), δ_{H} 4.43 (1H, dd, $^3J_{\text{HH}} = 6.4, 7.8$ Hz, 4-H), 5.04 (2H, s, CH_2Ph), 5.71 (1H, dd, $^3J_{\text{HH}} = 6.4$ Hz, $^4J_{\text{HH}} = 1.1$ Hz, 5-H), 7.28–7.37 (6H, m, 6H of Ar), 7.38 (1H, br s, 1'-H), 7.44–7.59 (7H, m, 7H of Ar), 8.05 (1H, d, $^3J_{\text{HH}} = 7.8$ Hz, NHCOOBn). ^{13}C NMR (75.5 MHz, DMSO- d_6), δ_{C} 61.3, 66.6, 76.8, 128.7, 128.8, 128.9, 129.1, 129.2, 129.4, 130.2, 130.4, 130.8, 133.3, 134.5, 137.1, 137.6, 156.8, 179.9. MS, $m/z = 468$ (MH^+), HRMS (ESI), $m/z = 468.0886$ (MH^+), $\text{C}_{24}\text{H}_{19}\text{Cl}_2\text{N}_3\text{O}_3$ requires 468.0882. Anal. Calcd for $\text{C}_{24}\text{H}_{19}\text{Cl}_2\text{N}_3\text{O}_3 \cdot \frac{1}{8}\text{H}_2\text{O}$ (470.58): C, 61.26; H, 4.12; N, 8.93%. Found: C, 60.94; H, 3.92; N, 9.32%.

3-Amino-5-benzylimidazolidine-2,4-dione (4). A mixture of **2** (311 mg, 1 mmol), ethanol (20 mL), and 10% Pd-C (100 mg) was hydrogenated (3 bar of H_2) at r.t. for 30 h. The catalyst was removed by filtration through a fritted funnel, washed with ethanol (2×5 mL), and the combined filtrate was evaporated in vacuo. The residue was purified by CC (column dimensions: 3×10 cm). First, the impurities were eluted with CH_2Cl_2 (100 mL), 10% *i*-PrOH/ CH_2Cl_2 (100 mL), and 10% EtOH/ CH_2Cl_2 (100 mL). Then the product was eluted with 20% EtOH/ CH_2Cl_2 (200 mL). Fractions containing the product were combined and evaporated in vacuo. Pale beige solid, yield 69%, 142 mg, mp 203–205 °C (from 20% $\text{H}_2\text{O}/i$ -PrOH), lit.^{11a} mp 205–206 °C (from EtOH), lit.^{12c} mp 204–205 °C (from 20% $\text{H}_2\text{O}/i$ -PrOH), R_{f} (EtOAc) 0.0, R_{f} (20% EtOH/EtOAc) 0.27, IR (ν_{max} , cm^{-1}): 3424, 2974, 2942, 2804, 2760, 2739, 2677, 2491, 1720 (C=O), 1704 (C=O), 1641, 1474, 1433, 1398, 1365, 1288, 1171, 1069, 1036, 849, 805, 762, 701 cm^{-1} . ^1H NMR (300 MHz, DMSO- d_6), δ_{H} 2.89 (1H, dd, $^3J_{\text{HH}} = 5.9, 14.1$ Hz, 1H of CH_2Ph), 2.99 (1H, dd, $^3J_{\text{HH}} = 4.9, 14.1$ Hz, 1H of CH_2Ph), 4.30 (1H, ddd, $^3J_{\text{HH}} = 1.4, 4.9, 5.9$ Hz, 5-H), 4.57 (2H, br s, NH_2), 7.15–7.34 (5H, m, Ph), 8.09 (1H, br s, NH). ^{13}C NMR (75.5 MHz, DMSO- d_6), δ_{C} 56.6, 65.5, 127.3, 127.9, 128.2, 136.8, 163.5, 171.9. MS, $m/z = 206$ (MH^+), HRMS (ESI), $m/z = 206.0927$ (MH^+), $\text{C}_{10}\text{H}_{12}\text{N}_3\text{O}_2$ requires 206.0930.

Thermal ‘ring switching’ transformation of azomethine imines (3a,b). General procedure for the preparation of 5-benzylidene-3-(benzylideneamino)hydantoins (8a,b)

A mixture of **3** (1 mmol) and anisole (5 mL) was heated under reflux for 5 h and volatile components were evaporated in vacuo. The solid residue was triturated with toluene (5 mL) and the precipitate was collected by filtration.

(Z)-5-Benzylidene-3-[(E)-benzylideneamino]imidazolidine-2,4-dione (8a). Prepared from **3a** (399 g, 1 mmol). White solid, yield 83%, 241 mg, mp 238–241 °C, lit.¹⁴ mp 187 °C, R_f (EtOAc) 0.37, IR (ν_{\max} , cm^{-1}): 3440, 3202, 3061, 1746 (C=O), 1713 (C=O), 1674, 1659, 1605, 1571, 1457, 1399, 1349, 1310, 1258, 1161, 1135, 1036, 970, 876, 754, 683, 650. ^1H NMR (300 MHz, DMSO- d_6), δ_{H} 6.65 (1H, s, C=CH), 7.25–7.57 (6H, m, 6H of Ph), 7.64–7.72 (2H, m, 2H of Ph), 7.82–7.89 (2H, m, 2H of Ph), 9.34 (1H, s, N=CH), 11.08 (1H, s, NH). ^{13}C NMR (75.5 MHz, DMSO- d_6), δ_{C} 110.9, 124.7, 127.7, 128.0, 128.8, 129.0, 129.7, 131.7, 132.6, 133.3, 151.9, 158.8, 160.5. MS, $m/z = 292$ (MH^+), HRMS (ESI), $m/z = 292.1096$ (MH^+), $\text{C}_{17}\text{H}_{14}\text{N}_3\text{O}_2$ requires 292.1086. Anal. Calcd for $\text{C}_{17}\text{H}_{13}\text{N}_3\text{O}_2 \cdot \frac{1}{4}\text{H}_2\text{O}$ (295.81): C, 69.03; H, 4.60; N, 14.21%, Found: C, 69.12; H, 4.54; N, 14.05%.

(Z)-5-Benzylidene-3-[(E)-(2,6-dichlorobenzylidene)amino]imidazolidine-2,4-dione (8b). Prepared from **3b** (468 g, 1 mmol). White solid, yield, 82%, 296 mg, mp 240–245 °C, R_f (EtOAc) 0.35, IR (ν_{\max} , cm^{-1}): 3448, 3237, 3113, 1775 (C=O), 1722 (C=O), 1656, 1603, 1580, 1456, 1389, 1368, 1355, 1316, 1256, 1186, 1138, 1094, 990, 951, 775, 755, 681, 650, 613, 602. ^1H NMR (300 MHz, DMSO- d_6), δ_{H} 6.67 (1H, s, C=CH), 7.36–7.48 (3H, m, 3H of Ph), 7.49–7.52 (1H, m, 1H of Ph), 7.60–7.65 (2H, m, 2H of Ph), 7.67–7.82 (2H, m, 2H of Ph), 9.66 (1H, s, N=CH), 11.16 (1H, s, NH). ^{13}C NMR (75.5 MHz, DMSO- d_6), δ_{C} 112.3, 125.3, 129.7, 129.8, 130.1, 130.6, 130.8, 133.0, 133.4, 134.9, 152.4, 154.0, 161.5. MS, $m/z = 360$ (MH^+), HRMS (ESI), $m/z = 360.0308$ (MH^+), $\text{C}_{17}\text{H}_{11}\text{Cl}_2\text{N}_3\text{O}_2$ requires 360.0307. Anal. Calcd for $\text{C}_{17}\text{H}_{11}\text{Cl}_2\text{N}_3\text{O}_2$ (360.19): C, 56.69; H, 3.08; N, 11.67%. Found: C, 56.54; H, 3.00; N, 11.61%.

X-Ray structure analysis for compound (8a)

Single crystal X-ray diffraction data of compound **8a** were collected at room temperature on a Nonius Kappa CCD diffractometer using the Nonius Collect Software.¹⁶ DENZO and SCALEPACK¹⁷ were used for indexing and scaling of the data and the structure was solved by means of SIR97.¹⁸ Refinement and plotting were done using Xtal3.6¹⁹ program package. Crystal structure was refined on F values using the full-matrix least-squares procedure. The non-hydrogen atoms were refined anisotropically, while the positions of hydrogen atoms were geometrically calculated and their positional and isotropic atomic displacement parameters were not refined. Crystallographic data (excluding structure factors) for compound **8a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 787638. Copy of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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