1,3-Dipolar Cycloadditions of (1Z,4R*,5R*)-4-Benzamido-3-oxo-5-phenylpyrazolidin-1-ium-2-ides to Ethyl Propiolate

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1,3-Dipolar cycloadditions of (1Z,4R*,5R*)-4-benzamido-3-oxo-5-phenylpyrazolidin-1-ium-2-ides 3a – e to ethyl propiolate (4) were studied. The reactions were carried out in anisole under reflux and in anisole under microwave irradiation at 150 °C. All reactions were quite non-selective and furnished mixtures of isomeric cycloadducts, 5, 5′, 6, and 6′, with ethyl (1S*,6R*,7R*)-6-benzamido-1-(4-nitrophenyl)-5-oxo-7-phenyl-1,5,6,7-tetrahydropyrazolo[1,2-a]pyrazole-2-carboxylates 5a – e as the major isomers. Pure major isomers 5a – e were obtained in low to moderate yields upon thorough chromatographic workup (CC followed by MPLC). The structures of cycloadducts 5, 5′, 6, and 6′ were determined by 1H NMR and NOESY spectroscopy.

Key words: 3-Pyrazolidinones, Azomethine Imines, Ethyl Propiolate, Cycloadditions, Stereochemistry

Introduction

1,3-Dipolar cycloadditions are powerful methods for the preparation of five-membered heterocycles, since they enable access to various polyfunctionalized chiral compounds with multiple asymmetric centers, usually with excellent stereocontrol [1]. Within this context, several examples of asymmetric cycloadditions in cyclic chiral azomethine imine series have also been reported. Generally, these reactions were accompanied by high facial and endo/exo-selectivity and afforded the corresponding fused pyrazolines with a bridgehead N–N structural element [2 – 12].

The importance of pyrazolidin-3-ones has increased significantly in the last decade, due to their applicability in industrial processes, and because several pyrazolidin-3-one derivatives exhibit biological activities [13, 14]. Recently, 3-pyrazolidinones have also been employed as templates in enantioselective Diels-Alder [15] and Michael [16] reactions. An important group of fused pyrazolidinone analogs are 2-acylamino-1-oxo-1H,5H-pyrazolo[1,2-a]pyrazole-7-carboxylates, which are useful scaffolds for the preparation of conformationally constrained peptide mimetics, such as Eli-Lilly’s pyrazol[1,2-a]-pyrazolone based γ-lactam antibiotics LY 186826, LY 193239, and LY 255262 [17, 18]. Some examples of important 3-pyrazolidinones are depicted in Fig. 1.

Since the first reports of Dorn [19] and Oppolzer [20], 1,3-dipolar cycloaddition of pyrazolidin-3-one derived azomethine imines to acetylenic and olefinic dipolarophiles represents a common method for the preparation of pyrazolo[1,2-a]pyrazolones. Most of the early studies were performed on achiral and on poorly substituted chiral dipoles [13, 14, 17], while recent studies established also the applicability of chiral polysubstituted 3-pyrazolidinone-1-azomethine imines in the stereoselective synthesis
of highly functionalized pyrazolo[1,2-a]pyrazolones [4–11].

In the last decade, a part of our research interest has been devoted to the chemistry of 3-pyrazolidinones and their fused analogs [4, 8–11, 21–23]. Within this context, we have previously reported 1,3-dipolar cycloadditions of azomethine imines derived from (4R*,5R*)-4-benzoylamino-5-phenyl-3-pyrazolidinone (1) and aromatic aldehydes 2. Generally, these cycloadditions were highly stereoselective and stereochemistry was controlled by the stereo-directing group in the chiral dipole, by the ortho-substituents at the aromatic ring, and by the structure of the dipolarophile [4, 8]. In extension, stereoselective combinatorial cycloadditions of these azomethine imines to maleimides [9] and β-keto esters [10] have also been reported. In continuation of our work in this field, we herein report the results of our study on cycloadditions of (1Z,4R*,5R*)-4-benzamido-3-oxo-5-phenylpyrazolidin-1-ium-2-ides 3a–e to ethyl propiolate (4).

**Results and Discussion**

Azomethine imines 3a–e were prepared by a parallel solution-phase synthesis from the pyrazolidinone 1 and aromatic aldehydes 2a–e according to the literature procedure [9] (Scheme 1). Cycloadditions of dipoles 3a–e to ethyl propiolate (4) were first carried out under microwave irradiation in anisole at 150 °C. All reactions were quite non-selective and furnished the corresponding mixtures of the isomeric cycloadducts 5/5′/6/6′a–e. Primary purification of the crude reaction mixtures by flash chromatography (FC) furnished pure compounds 5a and 5d in 28 % and 8 % yield, respectively, and purified mixtures of isomeric cycloadducts 5/5′/6/6′b, c, e. Additional purification of these isomeric mixtures by medium-pressure liquid chromatography (MPLC) then furnished pure major isomers 5b, c, e in 15–32 % yield (Scheme 1, Table 1).

Formation of the major regioisomers 5/5′ from all dipoles 3 was not surprising, since the electronic distribution in azomethine imines 3 is reflected at best

![Scheme 1. Reaction Conditions: (i) ArCHO 2a–e, EtOH, CF₃COOH (cat.), reflux (ref. 9); (ii) ethyl propiolate (4), anisole, microwave irradiation (300 W, 150 °C); (iii) flash column chromatography (FC); (iv) medium-pressure liquid chromatography (MPLC).](image-url)
Table 1. Selected experimental data for mixtures of isomeric cycloadducts 5/5′/6/6′a–e.

<table>
<thead>
<tr>
<th>Compound Ar</th>
<th>Ratio of isomers</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5′:5:6:6′</td>
<td>5′:6:5′:6′</td>
</tr>
<tr>
<td>5/5′/6/6′a</td>
<td>4-nitro-phenyl</td>
<td>55:7:34:4</td>
</tr>
<tr>
<td>5′/6/6′b</td>
<td>4-methoxy-phenyl</td>
<td>61:9:20:10</td>
</tr>
<tr>
<td>5′/6/6′c</td>
<td>phenyl</td>
<td>48:21:31:0</td>
</tr>
<tr>
<td>5′/6/6′d</td>
<td>2,6-dichloro-phenyl</td>
<td>36:10:29:25</td>
</tr>
<tr>
<td>5′/6/6′e</td>
<td>2,4,6-trimethyl-phenyl</td>
<td>57:20:17:6</td>
</tr>
</tbody>
</table>

a Determined from the crude reaction mixture by 1H NMR; b isomerically pure compound; c obtained upon separation by MPLC; d upon microwave irradiation in anisole at 150 °C; e upon conventional heating in anisole under reflux.

Scheme 2.

by the resonance forms 3 and 3′ as the negative charge at the N(2) atom is stabilized by the carbonyl group (Scheme 2). Cycloadditions of ortho-unsubstituted dipoles 3a–c to 4 furnished both regioisomeric cycloadducts 5/5′a–c and 6/6′a–c in a ratio of ~ 2:1, respectively. This was in agreement with the regioselectivity observed in cycloadditions of ortho-unsubstituted 1-arylmethylidene-5,5-dimethyl-3-pyrazolidinone-1-azomethine imines to methyl propiolate [22b]. Similarly, formation of the major (1S∗,6S∗,7S∗)-isomers 5a–c with syn-oriented 1-H and 7-H was in agreement with stereocontrol, established previously in cycloadditions of ortho-unsubstituted dipoles 3a–c to other dipolarophiles [8–10]. Dipoles 3a–c can adopt a planar conformation 3* allowing both regioisomeric transition states for the concerted 1,3-dipolar cycloaddition. In terms
of facial selectivity, conformation 3\textsuperscript{a} favors attack of the dipolarophile from the less hindered (1\textsuperscript{R}Re)-face. In summary, formation of the major (1\textsuperscript{S},6\textsuperscript{R},7\textsuperscript{R})-isomers 5a–c is explainable by the concerted 1,3-dipolar cycloaddition mechanism [24] via preferential approach of 4 from the less hindered (1\textsuperscript{R}Re)-face of the (Z)-dipoles 3\textsuperscript{a}a–c (Scheme 2, Path A).

On the other hand, the outcome in cycloadditions of ortho-disubstituted dipoles 3d and 3e to ethyl propiolate (4) was quite surprising. Thus, cycloaddition of dipole 3d to 4 was regioselective and gave the 2-COOEt regioisomer 5/5\textsuperscript{d}, exclusively, while reaction of 3e furnished both regioisomers, 5/5\textsuperscript{e} and 6e, in a ratio of \( \sim 3 : 1 \) (c.f. Scheme 1, Table 1). This was in agreement with the high regioselectivity observed in cycloadditions of analogous ortho-disubstituted dipole to methyl propiolate [22b]. Furthermore, microwave-assisted cycloadditions of dipoles 3d and 3e with two ortho-substituents followed the same stereocontrol as reactions of their ortho-unsubstituted analogs 3a–c: (1\textsuperscript{R},6\textsuperscript{R},7\textsuperscript{R})-isomer 5\textsuperscript{d} and (1\textsuperscript{S},6\textsuperscript{R},7\textsuperscript{R})-isomer 5e were obtained as the major isomers (c.f. Scheme 1, Table 1). This was not in agreement with stereocontrol in cycloadditions of ortho-disubstituted dipoles 3d and 3e to other dipolarophiles, where cycloadducts with anti-oriented 1-H and 7-H were formed as the major diastereomers [8–10]. Therefore, a two step addition-cyclization mechanism proposed previously for reactions of 3d and 3e with other dipolarophiles [8, 9, 22b] is not applicable to reactions with ethyl propiolate (4). The simplest explanation for this unexpected selectivity could be that microwave irradiation enables the ortho-disubstituted dipoles 3d, e to adopt a planar conformation 3\textsuperscript{a}. Consequently, cycloadditions of dipoles 3d, e exhibit the same regiochemistry and stereochemistry as cycloadditions of their ortho-unsubstituted analogs 3a–c (Scheme 2, Path A).

In order to prove this hypothesis, additional experiments were performed. First, reactions of dipoles 3a–e with ethyl propiolate (4) were carried out by conventional heating in anisole under reflux. Quite unexpectedly, the ratios of ortho-unsubstituted isomers 5/5/6/6\textsuperscript{a}–c did not change much, while the ratio of isomers changed significantly in the case of two ortho-substituents: from 5/5\textsuperscript{e} > 3 : 1 in the presence of microwaves to 5/5\textsuperscript{e} > 3 : 1 under conventional heating (Table 1). Decreased facial selectivity under conventional heating was in agreement with the above proposed microwave-induced planarization of ortho-disubstituted dipoles 3d and 3e. Namely, in the absence of microwave activation a planar conformation 3\textsuperscript{a} is not accessible for dipoles 3d, e with two ortho-substituents. Since both faces are strongly hindered by the two ortho-substituents, facial selectivity is lost and almost equal amounts of diastereomers 5 and 5\textsuperscript{e} are obtained (Scheme 2, Path B). Then, ortho-disubstituted dipole 3d was reacted with dimethyl acetylenedicarboxylate (7) and dimethyl maleate (8) under microwave irradiation in anisole at 150 °C. Both reactions were highly selective and furnished the corresponding cycloadducts 9 and 10 as single isomers. However, compounds 9 and 10 were identical to those prepared previously under conventional heating in anisole [8] (Scheme 3). These experimental data lead to a conclusion that the different selectivity of cycloadditions of dipoles 3a–e to ethyl propiolate (4) is probably due to the shape and properties of the dipolarophile. On the other hand, the influence of microwaves on the stereocenters was not confirmed.

The structures of novel compounds 5a–e, 5\textsuperscript{a}–e, 6a–e, and 6\textsuperscript{a}–c were determined by spectroscopic (NMR, IR, MS) methods and by elemental analyses for C, H, and N. The major isomers 5a–e were isolated in isomerically pure form and fully characterized. The minor isomers 5\textsuperscript{a}–e, 5\textsuperscript{a}–e, 6a–e, and 6\textsuperscript{a}–c were isolated as mixtures of isomers and were characterized only by MS and NMR. The relative configurations of all isomeric cycloadducts, 5, 5\textsuperscript{e}, 6, and 6\textsuperscript{e}, were determined by NOESY spectroscopy.
by correlation of chemical shifts, and by correlation of vicinal coupling constants, $^3J_{H-H}$. The configuration at the newly formed stereocenter at position 1 was essential for the structure determination. The syn-orientation between 1-H and 7-H in compounds $5a$–$e$ and $6b$, $c$, $e$ was established on the basis of NOE between these two nuclei. In isomers $5' b$, $c$, $e$ and $6' c$, on the other hand, the absence of NOE between 1-H and 7-H was in agreement with the anti-orientation between these two nuclei. Accordingly, the (1$R^*$)-configuration was assigned to isomers $5'$ and $6'$, while the (1$S^*$)-configuration was assigned to isomers $5$ and $6$. The structures of compounds $5a$–$e$, $5'a$–$e$, $6a$–$e$, and $6'a$–$c$ were additionally confirmed by the correlation of the chemical shifts for 1-H, 2-H, 3-H, 5-H, 6-H, and 7-H and by correlation of the coupling constants $^3J_{H3-H1}$, $^4J_{H1-H3}$, and $^3J_{H6-H7}$. The regiochemistry of the cycloadducts was determined on the basis of the NMR data of the olefinic proton. In the 2-COOEt regioisomer $5/5'$, the olefinic proton 3-H appeared as a doublet at $\delta \sim 7.6$ ppm with the coupling constant $^4J_{H1-H3} = 0.9$ – 2.0 Hz. In the 3-COOEt regioisomer $6/6'$, the olefinic proton 2-H appeared at $\delta \sim 6.2$ ppm as a doublet with the vicinal coupling constant $^3J_{H2-H3} = 2.3$ – 2.8 Hz (Fig. 2, Table 2).

Table 2. Selected NMR data for compounds $5$, $5'$, $6$, and $6'$.

<table>
<thead>
<tr>
<th>Regioisomers</th>
<th>$\delta$ (ppm)</th>
<th>$^3J_{H1-H3}$ (Hz)</th>
<th>NOE (%)a</th>
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<tbody>
<tr>
<td>2-COOEt</td>
<td>1-H</td>
<td>2-H</td>
<td>3-H</td>
</tr>
<tr>
<td>$5a$</td>
<td>5.40</td>
<td>7.73</td>
<td>4.71</td>
</tr>
<tr>
<td>$5b$</td>
<td>5.23</td>
<td>7.68</td>
<td>4.75b</td>
</tr>
<tr>
<td>$5c$</td>
<td>5.20</td>
<td>7.71</td>
<td>4.75b</td>
</tr>
<tr>
<td>$5d$</td>
<td>6.28</td>
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<tr>
<td>$5'a$</td>
<td>5.55</td>
<td>c</td>
<td>c</td>
</tr>
<tr>
<td>$5'b$</td>
<td>5.43</td>
<td>7.76</td>
<td>4.93</td>
</tr>
<tr>
<td>$5'c$</td>
<td>5.50</td>
<td>7.80</td>
<td>4.92</td>
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<tr>
<td>$5'd$</td>
<td>6.46</td>
<td>c</td>
<td>5.39</td>
</tr>
<tr>
<td>$5'e$</td>
<td>5.93</td>
<td>7.63</td>
<td>5.02</td>
</tr>
<tr>
<td>3-COOEt</td>
<td>1-H</td>
<td>2-H</td>
<td>3-H</td>
</tr>
<tr>
<td>$6a$</td>
<td>5.37</td>
<td>6.07</td>
<td>5.08</td>
</tr>
<tr>
<td>$6b$</td>
<td>5.15</td>
<td>6.13</td>
<td>4.99</td>
</tr>
<tr>
<td>$6c$</td>
<td>5.23</td>
<td>6.18</td>
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<td>$6d$</td>
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<td>$6e$</td>
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<td>4.92</td>
</tr>
<tr>
<td>$6'a$</td>
<td>c</td>
<td>6.27</td>
<td>c</td>
</tr>
<tr>
<td>$6'b$</td>
<td>5.27</td>
<td>6.33</td>
<td>c</td>
</tr>
<tr>
<td>$6'c$</td>
<td>5.32</td>
<td>6.35</td>
<td>5.08</td>
</tr>
</tbody>
</table>

a Relative intensity with respect to $-100$% intensity of the irradiated proton; b overlapping signals for 6-H and 7-H appeared as a multiplet; c overlapped by other signals.

Fig. 2. Structure determination by NOESY spectroscopy.
Conclusion

Microwave-assisted cycloadditions of (1Z,4R*,5R*)-1-arylmethylene-4-benzoylamo-5-phenyl-3-pyrazolidinon-1-azomethine imines 3a–e to ethyl propiolate (4) were much less selective than previously described cycloadditions to other dipolarophiles [8–10]. Regiocontrol and stereocontrol of cycloadditions to ethyl propiolate (4) can be summarized in the following way: (a) all cycloadditions furnished the major 2-COOEt regioisomer 5/S' and (b) all cycloadditions gave the major (1S*,6R*,7R*)-diastereomer 5 with syn-oriented aryl groups at positions 1 and 7. Thus, regiochemistry and stereochemistry of cycloadditions of ortho-unsubstituted dipoles 3a–c was in agreement with that observed previously in closely related reactions, while stereochemistry of cycloadditions of ortho-disubstituted dipoles was not [8–10, 22b]. Further studies on reactions of dipoles 3 with terminal acetylenes, aiming on improved selectivity and possible combinatorial applications, are currently in progress.

Experimental Section

Melting points were determined on a Kofler micro hot stage. The NMR spectra were obtained on a Bruker Avance DPX 300 instrument at 300 MHz for 1H and 75.5 MHz for 13C, using [D6]DMSO and CDCl3 with TMS as the internal standard. Mass spectra were recorded on an AutoSpecQ and a Q-TOF Premier spectrometer, IR spectra on a Perkin-Elmer Spectrum BX FTIR spectrophotometer. Microanalyses were performed on a Perkin-Elmer CHN Analyzer 2400 II. Flash chromatography (FC) was performed on silica gel (Fluka, silica gel 60, 0.04 – 0.06 mm). Medium-pressure liquid chromatography (MPLC) was performed with a Büchi isocratic system with detection on silica gel (Merck, silica gel 40, 0.015 – 0.035 mm); column dimensions (dry filled): 15 x 460 mm; backpressure: 10 – 15 bar; detection: UV 254 nm; sample amount: 100 – 150 mg of isomeric mixture per run. The isomer ratios were determined by 1H NMR spectroscopy. Ethyl propiolate (4) is commercially available (Sigma Aldrich). Azomethine imines 3a–e were prepared according to the literature procedure [9].

Microwave-assisted 1,3-dipolar cycloadditions of azomethine imines 3a–e to ethyl propiolate (4)

General procedure

A mixture of an azomethine imine 3a–e (1.0 mmol), ethyl propiolate 4 (0.111 mL, 1.1 mmol), and anisole (5 mL) was heated under microwave irradiation at 150 °C for 1 h. The reaction mixture was cooled, and volatile components were evaporated in vacuo. The residue was purified by FC (silica gel, ethyl acetate-hexanes). Fractions containing the products were combined and evaporated in vacuo to give isomerically pure cycloadducts 5a and 5d and mixtures of isomeric cycloadducts 5/S'/6/6'.c, e. The mixtures of isomers 5/S'/6/6'.b, c, e were separated by MPLC (ethyl acetate-hexanes). Fractions containing the products were combined and evaporated in vacuo to give isomerically pure cycloadducts 5b, 5c, and 5e and mixtures of isomeric cycloadducts 5/S'/6/6'.b, c, e.

The following compounds were prepared in this manner:

Ethyl (1S*,6R*,7R*)-6-benzamido-1-(4-nitrophenyl)-5-oxo-7-phenyl-1,5,6,7-tetrahydro-pyrazolo[1,2-a]pyrazole-2-carboxylate (5a), its (1R*,6R*,7R*)-epimer 5'a, and ethyl (1R*,6R*,7R*)-6-benzamido-1-(4-nitrophenyl)-5-oxo-7-phenyl-1,5,6,7-tetrahydro-pyrazolo[1,2-a]pyrazole-3-carboxylate (6a) and its (1S*,6R*,7R*)-epimer 6'a

A mixture of the title compounds (5a:5'a:6a:6'a = 55:7:34:4) was prepared from azomethine imine 3a (414 mg, 1 mmol); FC (ethyl acetate-hexanes, 1:1), 5a:5'a:6a:6'a = 100:0:0:0. Yield: 146 mg (28%) of a yellow solid; m. p. 124 – 126 °C – IR (KBr): ν = 3315 (NH); 1736, 1713, 1648 (C=O) cm⁻¹. 1H NMR (CDCl3): δ = 1.17 (3H, t, J = 7.1 Hz, CH2CH3), 3.99 – 4.20 (2H, m, CH2CH3), 4.71 (1H, dd, J = 7.5, 10.9, 6-H, 4.85 (1H, d, J = 10.9 Hz, 7-H), 5.40 (1H, d, J = 1.4 Hz, 1-H), 6.62 (1H, br d, J = 7.5 Hz, NH), 7.09 – 7.24 (5H, m, 5H-Ar), 7.35 – 7.48 (4H, m, 4H-Ar), 7.49 – 7.57 (1H, m, 1H-Ar), 7.71 – 7.79 (2H, m, 2H-Ar), 7.73 (1H, d, J = 1.4 Hz, 3-H), 8.02 – 8.08 (2H, m, 2H-Ar). – Anal. for C28H24N4O6: calcd. C 65.62, H 4.72, N 10.93; found C 65.66, H 4.92, N 10.74.

1H NMR data for the minor isomers 5a', 6a, and 6'a,

1H NMR (CDCl3), compound 5'a: δ = 5.55 (1H, d, J = 0.9 Hz, 1-H); compound 6a: δ = 4.65 (1H, d, J = 11.5 Hz, 7-H), 5.08 (1H, dd, J = 7.9, 11.5 Hz, 6-H), 5.37 (1H, d, J = 2.3 Hz, 1-H), 6.07 (1H, d, J = 2.4 Hz, 2-H); compound 6'a: δ = 6.27 (1H, d, J = 3.0 Hz, 2-H).

Ethyl (1S*,6R*,7R*)-6-benzamido-1-(4-methoxyphenyl)-5-oxo-7-phenyl-1,5,6,7-tetrahydro-pyrazolo[1,2-a]pyrazole-2-carboxylate (5b), its (1R*,6R*,7R*)-epimer 5'b, and ethyl (1R*,6R*,7R*)-6-benzamido-1-(4-methoxyphenyl)-5-oxo-7-phenyl-1,5,6,7-tetrahydro-pyrazolo[1,2-a]pyrazole-3-carboxylate (6b)

A mixture of the title compounds (5b:5'b:6b = 48:21:31) was prepared from azomethine imine 2b (400 mg, 1 mmol); FC (ethyl acetate-hexanes, 2:3). Subsequent separation by MPLC (ethyl acetate-hexanes, 2:3) afforded isomerically pure compound 5b.
**Data for compound 5b.** Yield: 71 mg (14%) of a yellow solid; m.p. 165–168 °C. – IR (KBr): v = 3329 (NH); 1735, 1707, 1647 (C=O); 1699, 1541, 1435, 1364, 1327, 1249, 966 cm⁻¹. – ¹H NMR (CDCl₃): δ = 1.16 (3H, t, J = 7.2 Hz, CH₂CH₃), 3.74 (3H, s, OMe), 3.99 – 4.18 (2H, m, CH₂CH₃), 4.70 – 4.81 (2H, m, 6-H, 7-H), 5.23 (1H, d, J = 1.9 Hz, 1-H), 6.56 (1H, d, J = 5.6 Hz, NH), 6.74 – 6.76 (2H, m, 2H-Ar), 7.01 – 7.09 (2H, m, 2H-Ar), 7.12 – 7.24 (5H, m, 5H-Ar), 7.38 – 7.46 (2H, m, 2H-Ar) – Anal. for C₂₉H₂₇N₃O₄: calcd. C 71.93, H 5.39, N 8.99; found C 72.21, H 5.52, N 8.88.

**Ethyl (1S*,6R*,7R*)-6-benzamido-5-oxo-1,7-diphenyl-1,5,6,7-tetrahydropyrazolo[1,2-a]pyrazole-2-carboxylate (5c), its (1R*,6R*,7R*)-epimer 5e, ethyl (1R*,6S*,7R*)-6-benzamido-5-oxo-1,7-diphenyl-1,5,6,7-tetrahydropyrazolo[1,2-a]pyrazole-2-carboxylate (6c), and its (1S*,6R*,7R*)-epimer 6e**

A mixture of the title compounds (5c: 5e: 6c: 6e = 36: 10: 29: 25) was prepared from azomethine imine (368 mg, 1 mmol); FC (ethyl acetate-hexanes, 1:2). Subsequent separation by MPLC (ethyl acetate-hexanes, 2:3) afforded isomerically pure compound 5c.

**Data for compound 5c.** Yield: 71 mg (15%) of a white solid; m.p. 119–122 °C. – IR (KBr): v = 3305, 3259 (NH); 1735, 1700, (C=O); 1636, 1606, 1536, 1425, 1365, 1330, 1282, 1256, 1231, 1198, 700 cm⁻¹. – ¹H NMR (CDCl₃): δ = 1.16 (3H, t, J = 7.2 Hz, CH₂CH₃), 4.03 and 4.09 (2H, 2dq, 1:1, J = 1.1 Hz, CH₂CH₃), 4.70 – 4.81 (2H, m, 6-H and 7-H), 5.26 (1H, d, J = 1.7 Hz, 1-H), 6.64 (1H, br s, NH), 7.10 – 7.25 (10H, m, 10H-Ar), 7.36 – 8.15 (2H, m, 2H-Ar), 7.48 – 7.54 (1H, m, 1H-Ar), 7.71 (1H, d, J = 1.7 Hz, 7-H), 7.72 – 7.76 (2H, m, 2H-Ar) – Anal. for C₂₉H₂₇N₃O₄; calcd. C 71.93, H 5.39, N 8.99; found C 72.21, H 5.52, N 8.88.

**Ethyl (1S*,6R*,7R*)-6-benzamido-5-oxo-1,7-diphenyl-1,5,6,7-tetrahydropyrazolo[1,2-a]pyrazole-2-carboxylate (5d), its (1S*,6R*,7R*)-epimer 5f, and ethyl (1R*,6R*,7R*)-6-benzamido-5-oxo-1,7-diphenyl-1,5,6,7-tetrahydropyrazolo[1,2-a]pyrazole-2-carboxylate (6f)**

A mixture of the title compounds (5d: 5f: 6d = 85: 15) was prepared from azomethine imine (2d (438 mg, 1 mmol); FC (ethyl acetate-hexanes, 1:2). 5d: 5f = 100: 0. Yield: 41 mg (8%) of a white solid; m.p. 189–191 °C. – IR (KBr): v = 3305, 3259 (NH); 1735, 1700, 1636, (C=O) cm⁻¹. – ELMS: m/z = 535 (M⁺). – ¹H NMR (CDCl₃): δ = 1.11 (3H, t, J = 7.2 Hz, CH₂CH₃), 4.06 and 4.10 (2H, 2dq, 1:1, J = 7.2, 10.8 Hz, CH₂CH₃), 4.74 (1H, dd, J = 7.2, 11.0 Hz, 6-H), 4.81 (1H, d, J = 11.0 Hz, 7-H), 6.28 (1H, d, J = 2.0 Hz, 1-H), 6.80 (1H, d, J = 7.2 Hz, NH), 6.92 – 7.24 (8H, m, 8-HAr), 7.39 – 7.46 (2H, m, 2H-Ar), 7.49 and 7.73 – 7.29 (2H, m, 2H-Ar). – ¹C NMR (CDCl₃): δ = 13.9, 21.4, 60.5, 62.9, 69.7, 74.6, 116.8, 125.2, 127.1, 127.2, 128.2, 128.5, 129.9, 132.0, 132.5, 132.8, 134.7, 136.1, 162.0, 162.64, 167.2. – Anal. for C₂₉H₂₇N₃O₄; calcd. C 71.69, H 4.32, N 7.83; found C 76.30, H 4.42, N 7.72. – HRMS: calcd. for C₂₉H₂₇N₃O₄, m/z = 535.1079 (M⁺); found m/z = 535.1066 (M⁺).

**Ethyl (1S*,6R*,7R*)-6-benzamido-1-(2,4,6-trimethyl-phenyl)-5-oxo-7-phenyl-1,5,6,7-tetrahydropyrazolo[1,2-a]pyrazole-2-carboxylate (5e), its (1S*,6R*,7R*)-epimer 5g, and ethyl (1R*,6R*,7R*)-6-benzamido-1-(2,4,6-trimethyl-phenyl)-5-oxo-7-phenyl-1,5,6,7-tetrahydropyrazolo[1,2-a]pyrazole-2-carboxylate (6e)**

A mixture of the title compounds (5e: 5f: 6e = 65: 15: 23) was prepared from azomethine imine (2e (438 mg, 1 mmol); FC (ethyl acetate-hexanes, 1:2). Subsequent separation by MPLC (ethyl acetate-hexanes, 1:2) afforded isomerically pure compound 5e.

**Data for compound 5e.** Yield: 133 mg (26%) of a pale yellowish solid; m.p. 135–136 °C. – IR (KBr): v = 3389 (NH); 1728, 1679 (C=O); 1769, 1593, 1491, 1435, 1369, 1327, 1252, 1239, 700 cm⁻¹. – ¹H NMR (CDCl₃): δ = 1.14 (3H, t, J = 7.2 Hz, CH₂CH₃), 1.85, 2.15 in 2.52 (9H, 3x, 1: 1: 1, 3x,Me), 3.99 – 4.16 (2H, m, CH₂CH₃), 4.67 (1H, dd, J = 7.5, 11.3 Hz, 6-H), 4.76 (1H, d, J = 11.3 Hz, 7-H), 5.78 (1H, d, J = 1.9 Hz, 1-H), 6.45 (1H, br s, 1H-C₆H₂), 6.54 (1H, br d, J = 7.5 Hz, NH), 6.75 (1H, br s, 1H-C₆H₂), 7.04 – 7.15 (5H, m, 5H-Ar), 7.40 – 7.47 (2H, m, 2H-Ar), 7.50 – 7.57 (1H, m, 1H-Ar), 7.64 (1H, d, J = 1.9 Hz, 1-H).
NH). 7.74 – 7.79 (2H, m, 2H-Ar). – Anal. for C_{23}H_{31}N_{3}O_{2}: calcd. C 73.06, H 6.13, N 8.25; found C 72.84, H 6.25, N 8.01.

\[{^1}H \text{ NMR data for the minor isomers } S' \text{ and } 6e. \] \([\text{CDCl}_3], \text{compound } S': \delta = 4.04 – 4.17 (2H, m, CH\_2\_CH\_3), 4.32 (1H, d, J = 10.5 Hz, 7-H), 5.02 (1H, dd, J = 7.8, 10.5 Hz, 6-H), 5.93 (1H, d, J = 1.6 Hz, 1-H), 6.45 (1H, d, J = 7.8 Hz, NH), 7.63 (1H, d, J = 1.6 Hz, 3-H); \text{compound } 6e: \delta = 4.29 – 4.46 (2H, m, CH\_2\_CH\_3), 4.60 (1H, d, J = 11.5 Hz, 7-H), 4.92 (1H, dd, J = 7.7, 11.5 Hz, 6-H), 5.67 (1H, d, J = 2.4 Hz, 1-H), 6.18 (1H, d, J = 2.4 Hz, 2-H), 6.69 (1H, d, J = 7.7 Hz, NH).

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[22] Syntheses from 5,5-dimethyl-3-pyrazolidinone:

[23] Synthesis of 3-phenylalanine analogs from 1: