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

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1,3-Dipolar cycloadditions of (1*Z*,4*R**,5*R**)-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 (1*S**,6*R**,7*R**)-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 ^{1}H 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-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-7-carboxylates, 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 [17, 18]. Some examples of important 3-pyrazolidinones are depicted in Fig. 1.

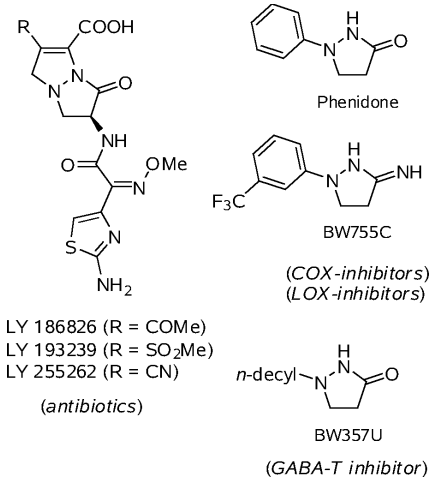
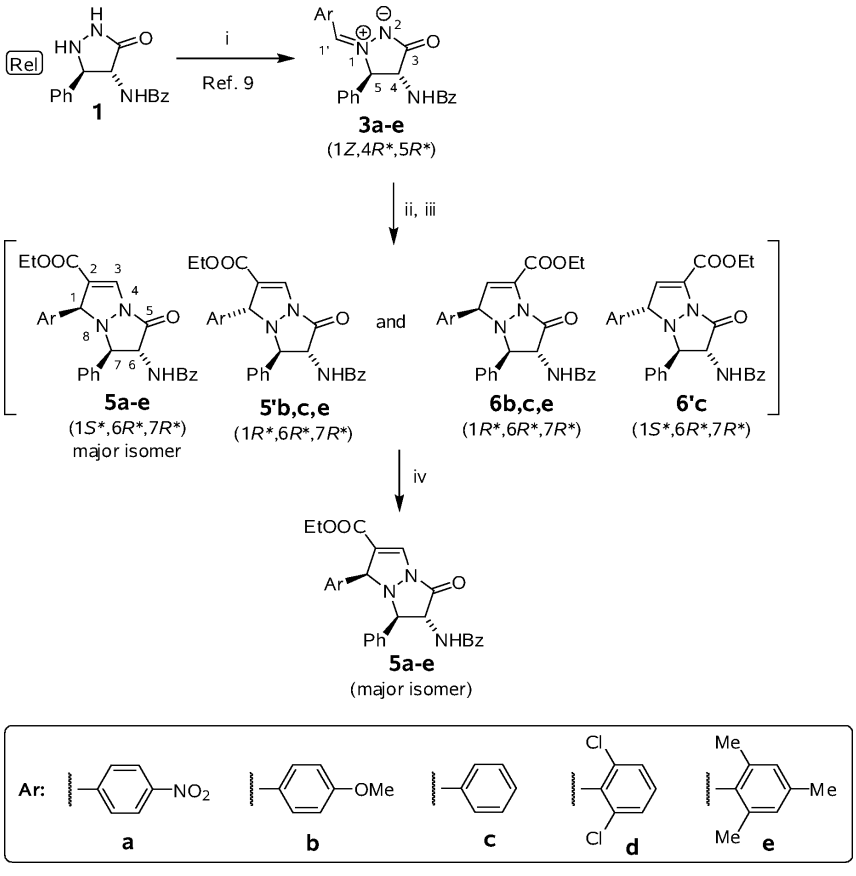


Fig. 1. Examples of important pyrazolidinones.

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



Scheme 1. Reaction Conditions: (i) ArCHO **2a** – **e**, EtOH, CF_3COOH (cat.), reflux (ref. 9); (ii) ethyl propiolate (**4**), anisole, microwave irradiation (300 W, 150 °C); (iii) flash column chromatograpy (FC); (iv) medium-pressure liquid chromatography (MPLC).

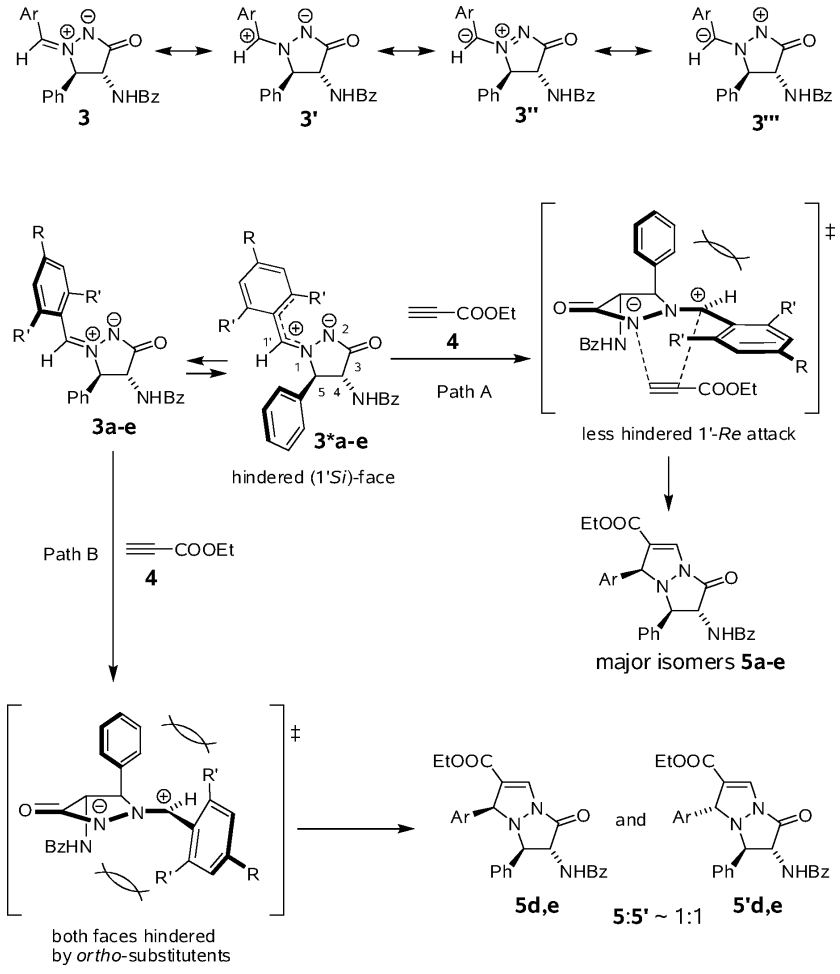
of highly functionalized pyrazolo[1,2-*a*]pyrazolones [4 – 11].

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 **3** derived from (4*R**,5*R**)-4-benzoylamino-5-phenyl-3-pyrazolidinone (**1**) and aromatic aldehydes **2**. Generally, these cycloadditions were highly stereoselective and stereochemistry was controlled by the stereodirecting 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 (1*Z*,4*R**,5*R**)-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



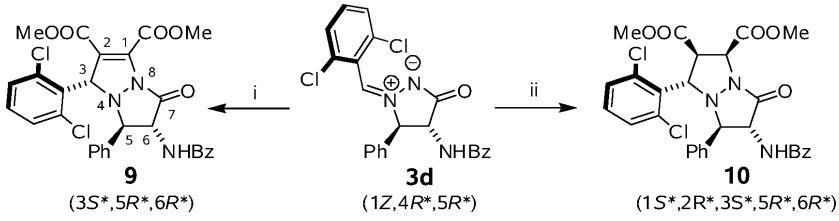
Scheme 2.

Table 1. Selected experimental data for mixtures of isomeric cycloadducts **5/5′/6/6′a – e**.

Compound	Ar	Ratio of isomers		Yield (%)[b]
		5 : 5′ : 6 : 6′[a]	**5/5′ : 6/6′**[a]	
5/5′/6/6′a	4-nitro-	55 : 7 : 34 : 4[d]	62 : 38[d]	28[d]
	phenyl	61 : 9 : 20 : 10[e]	69 : 30[e]	
5/5′/6/6′b	4-methoxy-	48 : 21 : 31 : 0[d]	69 : 31[d]	23[c,d]
	phenyl	57 : 20 : 17 : 6[e]	77 : 23[e]	
5/5′/6/6′c	phenyl	36 : 10 : 29 : 25[d]	46 : 54[d]	15[c,d]
		50 : 16 : 25 : 9[e]	66 : 34[e]	
5/5′/6/6′d	2,6-dichloro-	85 : 15 : 0 : 0[d]	100 : 0[d]	8[d]
	phenyl	53 : 47 : 0 : 0[e]	100 : 0[e]	
5/5′/6/6′e	2,4,6-trimethyl-	62 : 15 : 23 : 0[d]	77 : 23[d]	32[c,d]
	phenyl	53 : 43 : 4 : 0[e]	96 : 4[e]	

[a] Determined from the crude reaction mixture by ^{1}H 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.

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 (1*S**,6*S**,7*S**)-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



Scheme 3. Reaction Conditions: (i) dimethyl acetylenedicarboxylate (**7**), anisole, microwave irradiation (300 W, 150 °C); (ii) dimethyl maleate (**8**), anisole, microwave irradiation (300 W, 150 °C).

of facial selectivity, conformation **3*** favors attack of the dipolarophile from the less hindered (1′*Re*)-face. In summary, formation of the major (1*S**,6*R**,7*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′*Re*)-face of the (*Z*)-dipoles **3*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 regiospecific and gave the 2-COOEt regioisomer **5/5′d**, exclusively, while reaction of **3e** furnished both regioisomers, **5/5′e** and **6e**, in a ratio of $\sim 3:1$ (*c.f.* Scheme 1, Table 1). This was not in agreement with the high regioselectivity observed in cycloadditions of analogous *ortho*-disubstituted dipoles 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*R**,6*R**,7*R**)-isomer **5d*** and (1*S**,6*R**,7*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***. 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).

*Formally, the configurations at C(1) in compounds **5d** and **5e** are different due to chlorine atoms at the *ortho*-positions, which change the order of priority in compound **5d**. Essentially, the configuration at C(1) in all compounds **5a – e** is the same.

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 expectedly, the ratios of *ortho*-unsubstituted isomers **5/5′/6/6′a – c** did not change much, while the ratio of isomers changed significantly in the case of two *ortho*-substituents: from **5**:**5′** $> 3:1$ in the presence of microwaves to **5**:**5′** $\sim 1:1$ 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*** 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′** 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 **4**. On the other hand, the influence of microwaves on the stereocontrol was not confirmed.

The structures of novel compounds **5a – e**, **5′a – e**, **6a – e**, and **6′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′a – e**, **5′a – e**, **6a – e**, and **6′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′**, **6**, and **6′**, were determined by NOESY spectroscopy,

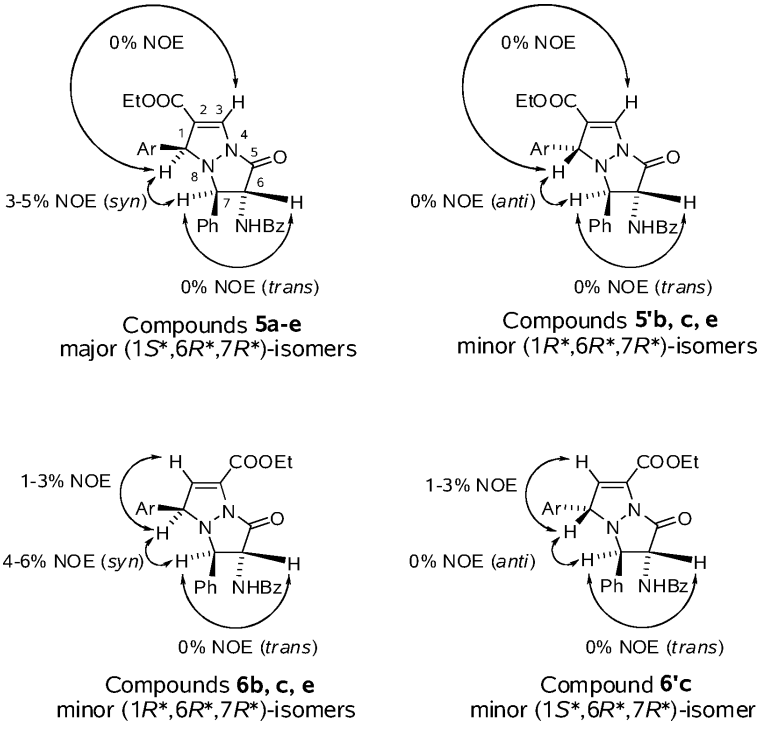


Fig. 2. Structure determination by NOESY spectroscopy.

Table 2. Selected NMR data for compounds **5**, **5′**, **6**, and **6′**.

	2-COOEt Regioisomers **5** and **5′**						
	δ (ppm)				$^3J_{H,H}$ (Hz)		NOE (%)[a]
	1-H	3-H	6-H	7-H	1 – 3	6 – 7	1 ··· 7
5a	5.40	7.73	4.71	4.85	1.4	10.9	4
5b	5.23	7.68	4.75[b]	4.75[b]	1.9	[b]	5
5c	5.20	7.71	4.75[b]	4.75[b]	1.7	[b]	5
5d	6.28	7.69	4.74	4.81	2.0	11.0	3
5e	5.78	7.64	4.67	4.76	1.9	11.3	4
5′a	5.55	[c]	[c]	[c]	0.9	–	–
5′b	5.43	7.76	4.93	3.96	0.9	11.2	0
5′c	5.50	7.80	4.92	3.95	1.1	11.2	0
5′d	6.46	[c]	5.39	4.32	1.6	10.8	–
5′e	5.93	7.63	5.02	4.32	1.6	10.5	0

	3-COOEt Regioisomers **6** and **6′**						
	δ (ppm)				$^3J_{H,H}$ (Hz)		NOE (%)[a]
	1-H	2-H	6-H	7-H	1 – 2	6 – 7	1 ··· 7
6a	5.37	6.07	5.08	4.65	2.3	11.5	–
6b	5.15	6.13	4.99	4.58	2.3	11.4	5
6c	5.23	6.18	5.19	4.60	2.4	11.5	4
6d	6.18	6.23	5.03	4.69	2.5	11.5	–
6e	5.67	6.18	4.92	4.60	2.4	11.5	6
6′a	[c]	6.27	[c]	[c]	3.0	–	–
6′b	5.27	6.33	[c]	[c]	2.9	–	–
6′c	5.32	6.35	5.08	3.82	2.8	11.5	0

[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.

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 $^3J_{H1-H2}$, $^4J_{H-H3}$, 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).

Conclusion

Microwave-assisted cycloadditions of (1*Z*,4*R**,5*R**)-1-arylmethylidene-4-benzoylamino-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 **5/5′** and (b) all cycloadditions gave the major (1*S**6*R**,7*R**)-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 ^{1}H and 75.5 MHz for ^{13}C, using [D$_6$]DMSO and $CDCl_3$ 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 × 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 ^{1}H 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 **5/5′/6/6′b**, **c**, **e**. The mixtures of isomers **5/5′/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′/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-tetrahydropyrazolo-[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}. – ^{1}H NMR ($CDCl_3$): δ = 1.17 (3H, t, J = 7.1 Hz, CH_2CH_3), 3.99 – 4.20 (2H, m, CH_2CH_3), 4.71 (1H, dd, J = 7.5, 10.9 Hz, 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 $C_{28}H_{24}N_4O_6$: calcd. C 65.62, H 4.72, N 10.93; found C 65.66, H 4.92, N 10.74.

*^{1}H NMR data for the minor isomers **5′a**, **6a**, and **6′a**.* ^{1}H NMR ($CDCl_3$), *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-tetrahydropyrazolo-[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**.

[†] Donation of the Alexander von Humboldt Foundation.

Data for compound ***5b***. Yield: 71 mg (14 %) of a yellow solid; m. p. 165 – 168 °C. – IR (KBr): ν = 3329 (NH); 1735, 1707, 1647 (C=O); 1609, 1541, 1514, 1433, 1364, 1327, 1249, 696 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.16 (3H, t, *J* = 7.2 Hz, CH_2CH_3), 3.74 (3H, s, OMe), 3.99 – 4.18 (2H, m, CH_2CH_3), 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), 6.67 – 6.74 (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), 7.48 – 7.55 (1H, m, 1H-Ar), 7.68 (1H, d, *J* = 1.9 Hz, 7-H), 7.72 – 7.77 (2H, m, 2H-Ar). – Anal. for $C_{29}H_{27}N_3O_5$: calcd. C 70.01, H 5.47, N 8.45; found C 70.18, H 5.64, N 8.29.

^1H NMR data for the minor isomers ***5′b****, 6b, and* ***6′b***. ^1H NMR ($CDCl_3$), *compound* ***5′b***: δ = 3.73 (3H, s, OMe), 3.96 (1H, d, *J* = 11.2 Hz, 7-H), 4.93 (1H, dd, *J* = 8.1, 11.1 Hz, 6-H), 5.43 (1H, d, *J* = 0.9 Hz, 1-H), 6.36 (1H, d, *J* = 8.1 Hz, NH), 7.76 (1H, d, *J* = 0.9 Hz, 7-H); *compound* ***6b***: δ = 3.79 (3H, s, OMe), 4.58 (1H, d, *J* = 11.4 Hz, 7-H), 4.99 (1H, dd, *J* = 7.7, 11.4 Hz, 6-H), 5.15 (1H, d, *J* = 2.3 Hz, 1-H), 6.13 (1H, d, *J* = 2.3 Hz, 2-H); *compound* ***6′b***: δ = 5.27 (1H, d, *J* = 2.9 Hz, 1-H), 6.33 (1H, d, *J* = 2.9 Hz, 1-H).

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* ***5′c****, ethyl (1R*,6R*,7R*)-6-benzamido-5-oxo-1,7-diphenyl-1,5,6,7-tetrahydropyrazolo [1,2-a]pyrazole-3-carboxylate (****6c****), and its (1S*,6R*,7R*)-epimer* ***6′c***

A mixture of the title compounds (**5c** : **5′c** : **6c** : **6′c** = 36 : 10 : 29 : 25) was prepared from azomethine imine **2c** (368 mg, 1 mmol); FC (ethyl acetate-hexanes, 2 : 3). 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): ν = 3305, 3259 (NH); 1735, 1700, (C=O); 1636, 1606, 1536, 1425, 1365, 1330, 1282, 1256, 1231, 1198, 700 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.16 (3H, t, *J* = 7.2 Hz, CH_2CH_3), 4.03 and 4.09 (2H, 2dq, 1 : 1, *J* = 7.2, 10.6 Hz, CH_2CH_3), 4.71 – 4.80 (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 – 45 (2H, m, 2H-Ar), 7.48 – 7.56 (1H, m, 1H-Ar), 7.71 (1H, d, *J* = 1.7 Hz, 7-H), 7.72 – 7.76 (2H, m, 2H-Ar). – Anal. for $C_{28}H_{25}N_3O_4$: calcd. C 71.93, H 5.39, N 8.99; found C 72.21, H 5.52, N 8.88.

^1H NMR data for the minor isomers ***5′c****, 6c, and* ***6′c***. ^1H NMR ($CDCl_3$), *compound* ***5′c***: δ = 3.95 (1H, d, *J* = 11.2 Hz, 7-H), 4.92 (1H, dd, *J* = 8.2, 11.2 Hz, 6-H), 5.50 (1H, d, *J* = 1.1 Hz, 1-H), 6.60 (1H, d, *J* = 8.1 Hz, NH); *compound* ***6c***: δ = 4.60 (1H, d, *J* = 11.5 Hz, 7-H), 5.19 (1H, dd, *J* = 8.0, 11.4 Hz, 6-H), 5.23 (1H, d, *J* = 2.4 Hz, 1-H), 6.18 (1H, d, *J* = 2.4 Hz, 2-H), 6.47 (1H, d, *J* = 8.1 Hz, NH); *compound* ***6′c***: δ = 3.82 (1H, d, *J* = 11.5 Hz, 7-H), 5.08 (1H, dd, *J* = 7.9, 11.4 Hz, 6-H), 5.32 (1H, d, *J* = 2.8 Hz, 1-H), 6.35 (1H, d, *J* = 2.8 Hz, 2-H), 6.43 (1H, d, *J* = 7.9 Hz, NH).

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

A mixture of the title compounds (**5d** : **5′d** = 85 : 15) was prepared from azomethine imine **2d** (438 mg, 1 mmol), FC (ethyl acetate-hexanes, 1 : 2), **5d** : **5′d** = 100 : 0. Yield: 41 mg (8 %) of a white solid; m. p. 189 – 191 °C. – IR (KBr): ν = 3305, 3259 (NH); 1735, 1700, 1636, (C=O) cm^{-1}. – EI-MS: *m/z* = 535 (M^+). – ^1H NMR ($CDCl_3$): δ = 1.11 (3H, t, *J* = 7.2 Hz, CH_2CH_3), 4.06 and 4.10 (2H, 2dq,1 : 1, J = 7.2, 10.8 Hz, CH_2CH_3), 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, 8H-Ar), 7.39 – 7.46 (2H, m, 2H-Ar), 7.48 – 7.56 (1H, m, 1H-Ar), 7.69 (1H, d, *J* = 2.0 Hz, 3-H), 7.73 – 7.79 (2H, m, 2H-Ar). – ^{13}C NMR ($CDCl_3$): 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, 128.9, 129.9, 132.0, 132.5, 132.8, 134.7, 136.1, 162.60, 162.64, 167.2. – Anal. for $C_{28}H_{23}Cl_2N_3O_4$: calcd. C 62.69, H 4.32, N 7.83; found C 63.30, H 4.42, N 7.72. – HRMS: calcd. for $C_{28}H_{23}Cl_2N_3O_4$, *m/z* = 535.1079 (M^+); found *m/z* = 535.1066 (M^+).

^1H NMR data for the minor isomer ***5′d***. ^1H NMR ($CDCl_3$), *compound* ***5′d***: δ = 4.32 (1H, d, *J* = 10.8 Hz, 7-H), 5.39 (1H, dd, *J* = 8.5, 10.8 Hz, 6-H), 6.46 (1H, d, *J* = 1.6 Hz, 1-H), 6.57 (1H, d, *J* = 8.5 Hz, NH).

Ethyl (1S,6R*,7R*)-6-benzamido-1-(2,4,6-trimethylphenyl)-5-oxo-7-phenyl-1,5,6,7-tetrahydropyrazolo[1,2-a] pyrazole-2-carboxylate (****5e****), its (1R*,6R*,7R*)-epimer* ***5′e****, and ethyl (1R*,6R*,7R*)-6-benzamido-1-(2,4,6-trimethylphenyl)-5-oxo-7-phenyl-1,5,6,7-tetrahydropyrazolo[1,2-a] pyrazole-3-carboxylate (****6e****)*

A mixture of the title compounds (**5e** : **5′e** : **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): ν = 3389 (NH); 1728, 1679 (C=O); 1679, 1593, 1491, 1435, 1369, 1327, 1252, 1239, 700 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.14 (3H, t, *J* = 7.2 Hz, CH_2CH_3), 1.85, 2.15 in 2.52 (9H, 3×s, 1 : 1 : 1, 3×Me), 3.99 – 4.16 (2H, m, CH_2CH_3), 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-C_6H_2), 6.54 (1H, br d, *J* = 7.5 Hz, NH), 6.75 (1H, br s, 1H-C_6H_2), 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,

3-H), 7.74 – 7.79 (2H, m, 2H-Ar). – Anal. for $C_{31}H_{31}N_3O_4$: calcd. C 73.06, H 6.13, N 8.25; found C 72.84, H 6.25, N 8.01.

[1]*H NMR data for the minor isomers* ***5′e*** *and* ***6e***. [1]H NMR ($CDCl_3$), *compound* ***5′e***: δ = 4.04 – 4.17 (2H, m, CH_2CH_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); *compound* ***6e***: δ = 4.29 – 4.46 (2H, m, CH_2CH_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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