Utilisation of chiral enaminones and azomethine imines in the synthesis of functionalised pyrazoles

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Abstract
Chiral enaminones, derived from commercially available enantipure starting materials, such as (+)-camphor and α-amino acids, were employed in cycloconensation reactions with hydrazine derivatives to afford the corresponding pyrazoles, functionalised with terpene, alanine, 2-phenylethylamine, and β-amino alcohol moiety. On the other hand, recent study on stereocontrol in cycloadditions of racemic (1Z,4R*,5R*)-1-arylmethyldene-4-benzoylamino-5-phenylpyrazolidin-3-one-1-azomethine imines, available in three steps from hippuric acid, showed, that stereodirecting phenyl group, as well as ortho-substituents at the aromatic ring, control the selectivity of these cycloadditions. In extension, these results are now applied in a study, which is oriented towards combinatorial synthesis of pyrazolo[1,2–a]pyrazolone type of peptidomimetics with variable, yet predictable configuration.

Keywords: Enaminones, heterocycles, azomethine imines, cyclisations, cycloadditions, chiral pool

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1. Introduction

Pyrazoles belong among the most representative five-membered heterocyclic systems.\(^1\) Despite the fact, that pyrazole ring is rarely a constituent of natural products, numerous synthetic pyrazole derivatives found use in various pharmaceutical, agrochemical, photographic, and other applications. Such examples of important pyrazole derivatives are natural products (\(S\))-pyrazolylalanine,\(^2\) pyrazomycin,\(^3\) and withasomine\(^4\) and synthetic compounds sildenafil (Viagra\(^®\)),\(^5\) lonazolac,\(^6\) difenamizole,\(^7\) mepirizole,\(^8\) phenidone,\(^9\) and bicyclic pyrazolidinone LY 186826.\(^10\)

On the other hand, synthesis and transformations of heterocyclic compounds represent the major topics of our research interest, which is primarily focused on development of synthetic methodologies for the preparation of various heterocyclic systems. In extension, these methodologies are then used for preparation of various types of heterocyclic compounds, which are functionalised with an amino acid, hydroxy acid, amino alcohol, polyl, nucleoside, terpene, dipeptide, and related structural motifs.\(^11\) Within this context, a part of our studies was also focused on the synthesis of functionalised pyrazoles. For this purpose, we used two 3+2 heterocyclisation approaches, which are, also in general, the most frequently employed methods for the formation of the pyrazole ring:

a) cyclocondensation between a hydrazine derivative and a suitably functionalised chiral enaminone as enmino masked 1,3-dicarbonyl compound analogue and
b) 1,3-dipolar cycloaddition of chiral 3-pyrazolidinone-1-azomethine imine to a suitable dipolarophile.

The present review represents a summary of our most recent results in the synthesis of functionalised pyrazoles.

2. Syntheses of functionalised pyrazoles from chiral enaminones

In the last two decades, a series of 2-substituted alkyl 3-(dimethylamino)propenoates 1 and related enaminones was synthesized and used for the preparation of various heterocyclic
systems, functionalised heterocycles, and natural product analogues.\textsuperscript{12,13} Recently, 3-(dimethylamino)propenoates 1 and analogs also found use in combinatorial synthesis.\textsuperscript{14} The most usual synthesis of alkyl 3-(dimethylamino)propenoates 1 consists of a treatment of an active methylene compound 2 with a formamide acetal. Propenoates 1 exhibit similar reactivity as their parent 1,3-dicarbonyl compounds: a) they react with electrophiles at position 2 and b) two electrophilic sites at positions 3 and 1 enable cyclisations with various 1,2- and 1,3-dinucleophiles leading to five- and six-membered heterocyclic systems. Reactions of 1 with nucleophiles are acid-catalysed and proceed by initial substitution of the dimethylamino group, followed condensation to the carbonyl group.\textsuperscript{12}

\begin{center}
\includegraphics[width=\textwidth]{scheme1.png}
\end{center}

Scheme 1
For example, in the reactions of 1 with hydrazine derivatives 3, substitution of the dimethylamino group takes place first to give the enehydrazines 4 (or tautomeric hydrazones 4'), followed by cyclisation to the carbonyl group to give the intermediate 5. In the case of enamino ketones (X = alkyl, aryl, etc.), elimination of water affords the 4,5-disubstituted pyrazole 6, while in the case of enamino esters and enamino amides, 4-substituted 5-hydroxypyrazoles 7 and/or their tautomers 7' are usually formed. In some cases, the intermediates 4/4' and 5' were isolated under mild reaction conditions and their structures were confirmed by X-Ray diffraction (Scheme 1).

In the chiral enamino series, our previous studies were based on transformations of 5-substituted lactams 8a,b and lactones 8c,d. Acid-catalysed reactions of 8a,b,d with various hydrazine derivatives 3, resulted in ‘ring switching’ formation of methyl (S)-N-acyl-3-(1-substituted-5-hydroxy-1H-pyrazol-4-yl)alanines 9a,b and (S)-1-O-benzoyle-3-(1-substituted-5-hydroxy-1H-pyrazol-4-yl)propane-1,2-diols 9c. In a recent extention, the ‘ring switching’ methodology was also applied in a parallel solution-phase synthesis of 3-pyrazolylalanines. On the other hand, when the dimethylamino group in enamiones 8a–c was substituted by the cyano group, nitriles 10a–c were obtained and used as chiral dipolarophiles in 1,3-dipolar cycloadditions to diazomethane and nitrile imines to afford spiro pyrazoles 11a–c and fused pyrazoles 12a,b with a dipeptide or closely related structural unit (Scheme 2).

Scheme 2. (i) R2NHNH2, AcOH, 80–120 °C; (ii) KCN, AcOH, r.t.; (iii) CH2N2–Et2O, 0 °C; (iii) ArC(Cl)=NNHPh, Et3N, CH2Cl2, reflux.

Similarly, 1-acyl-3-methyl-5-[(Z)-cyanomethylidene]imidazolidin-2,4-diones 13, available in three steps from hydantoin, reacted with diazomethane, azomethine imines, and nitrile imines to give, depending on the reaction conditions, the spiro pyrazole hydantoin and the pyrazole-5-carboxamide derivatives.
2.1 Synthesis of terpene-functionalised pyrazoles

Scheme 3. (i) t-BuOCH(NMe$_2$)$_2$, DMF, reflux; (ii) AcOOH, AcOH, AcONa, r.t.; (iii) R $\rightarrow$ NH$_2$ (3a,d–j), n-PrOH, 37% HCl (1 equiv.), reflux; (iv) R$^2$–NHNH$_2$ 3b,c, AcOH, reflux.

Recently, (1$R$,3$E$,4$R$)-3-[(dimethylamino)methylidene]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (16)$^{16}$ and (1$R$,4$E$,5$R$)-4-[(dimethylamino)methylidene]-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one (17)$^{24}$ were prepared from (+)-camphor (14). Reactions of 16 and 17 with hydrazines 3a–j afforded terpene-functionalised pyrazoles 18, 20, and 21. Reactions of 16 were selective and gave the corresponding pyrazolo fused camphors 18a–c. In the reaction of

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>Yield (%)</th>
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<tr>
<td>3a, 18a</td>
<td>H</td>
<td>81</td>
</tr>
<tr>
<td>3b, 18b</td>
<td>Benzyl</td>
<td>63</td>
</tr>
<tr>
<td>3c</td>
<td>6-chloropyridazin-3-yl</td>
<td>-</td>
</tr>
<tr>
<td>18c</td>
<td>6-oxo-1,6-dihydropyridazin-3-yl</td>
<td>83</td>
</tr>
<tr>
<td>3d, 20a</td>
<td>Ph</td>
<td>91</td>
</tr>
<tr>
<td>3e, 20b</td>
<td>3-methylphenyl</td>
<td>74</td>
</tr>
<tr>
<td>3f, 20c</td>
<td>4-methylphenyl</td>
<td>85</td>
</tr>
<tr>
<td>3a, 21a</td>
<td>H</td>
<td>83</td>
</tr>
<tr>
<td>3g, 21b</td>
<td>2-methylphenyl</td>
<td>70</td>
</tr>
<tr>
<td>3h, 21c</td>
<td>2-chlorophenyl</td>
<td>61</td>
</tr>
<tr>
<td>3i, 21d</td>
<td>2-bromophenyl</td>
<td>63</td>
</tr>
<tr>
<td>3j, 21e</td>
<td>Pentfluorophenyl</td>
<td>56</td>
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</table>
16 with 6-chloro-3-hydrazinopyridazine (3c), substitution of the chloro by the hydroxy group took place. On the other hand, reactions of the lactone analogue 17 proceeded in two ways. Treatment of 17 with ortho-unsubstituted phenylhydrazines 3d–f furnished the pyrazolo fused lactones 20a–c as products of elimination of water from the intermediate 19, while with ortho-substituted hydrazines 3g–j and with hydrazine hydrochloride (3a), opening of the lactone ring took place to give the ‘ring switched’ products 21a–e. It has to be emphasized, that also these reactions were highly selective and led to a single type of product, depending on the type of hydrazine derivative employed. Selectivity of these transformations might be attributed to steric, as well as to electronic effects (Scheme 3).25

2.2 Synthesis of (S)-3-(1-substituted-4-methoxycarbonyl-1H-pyrazol-5-yl)alanines from L-aspartic acid

\[
\begin{align*}
\text{HOOC} & \quad \text{COOBn} \quad \text{i} \quad \left[ \begin{array}{c}
\text{O} \\
\text{O} \\
\text{O} \\
\text{O}
\end{array} \right] \quad \text{COOBn} \\
\text{NHCOOBn} & \quad \text{ii}
\end{align*}
\]

\[
\begin{align*}
\text{MeOOC} & \quad \text{COOBn} \quad \text{iii} \quad \text{MeOOC} & \quad \text{COOBn} \\
\text{NHCOOBn} & \quad \text{iv}
\end{align*}
\]

\[
\begin{align*}
\text{MeOOC} & \quad \text{COOBn} \quad \text{v} \quad \text{MeOOC} & \quad \text{COOH} \\
\text{NHCOOBn} & \quad \text{NH2}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>Yield (%)</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>26</td>
<td>H</td>
<td>57</td>
<td>82</td>
</tr>
<tr>
<td>27</td>
<td>Ph</td>
<td>94</td>
<td>75</td>
</tr>
<tr>
<td>26a, 27a</td>
<td>H</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>26b, 27b</td>
<td>Ph</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>26c</td>
<td>pentafluorophenyl</td>
<td>85</td>
<td>82</td>
</tr>
<tr>
<td>26d, 27d</td>
<td>4-methoxyphenyl</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>26e, 27e</td>
<td>pyridin-2-yl</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>26f, 26g</td>
<td>6-phenylpyridazin-3-yl</td>
<td>80</td>
<td></td>
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Scheme 4. (i) Meldrum’s acid, DCC, CH₂Cl₂, DMAP, –5 °C (Ref. ); (ii) MeOH, reflux; (iii) DMFDMA, CH₂Cl₂, r.t.; (iv) R–NHNH₂ × HCl 3a,d,j–n, MeOH or EtOH, r.t.—reflux; (v) H₂ (1 bar), Pd–C, MeOH, r.t.
In search for alternative synthetic routes towards 3-pyrazolylalanines and other 3-heteroarylalanines, we have recently developed an enaminone-based methodology for the synthesis of (S)-3-((1H-pyrazol-5-yl)alanines. Starting from L-aspartic acid, the (S)-N-benzylxocarbonylaspartic acid-1-benzyl ester (22) was prepared according to the literature procedure. Following closely related literature examples, compound 22 was then coupled with Meldrum’s acid to give the intermediate 23, which was transformed with methanol into 1-benzyl-6-methyl (S)-2-benzylxocarbonylamino-4-oxohexanedioate (24) in 66% yield over two steps. Further treatment of 24 with N,N-dimethylformamide dimethyl acetal (DMFDMA) in dichloromethane at r.t. furnished the desired enaminone 25 in 98% yield. Cyclocondensations of 25 with substituted hydrazine hydrochlorides 3a,d,j–n gave the protected (S)-pyrazolylalanines 26a–g in 56–94% yields. Deprotection of 26a,b,e by catalytic hydrogenation furnished the free pyrazolylalanines 27a,b,e (Scheme 4).

2.3 Synthesis of pyrazoyl and pyrazolo[1,5-a]pyrimidinyl substituted 2-phenylethylamines and β-amino alcohols

2.3.1 Synthesis of L-3-phenylalanine and L-threonine derived enamino ketones

According to the literature known methodology, the N-protected L-3-phenylalanines 28a,b were transformed into the Weinreb amides 29a,b, which were then treated with excess ethynylmagnesium bromide. Upon quenching excess Grignard reagent with aqueous NaHSO₄, the corresponding ethynyl ketones 30a,b were obtained in 90 and 61% yield, respectively. Addition of diethylamine to the triple C≡C bond then afforded enamin ketones 31a,b in 92% and 86% yield, respectively. On the other hand, upon treatment of 29a with excess ethynylmagnesium bromide followed by quenching with aqueous NH₄Cl, the N-methyl-N-methoxy substituted enaminone 32 was obtained in 50% yield. Formation of 32 could be explained by initial formation of the ethynyl ketone 30a followed by addition of N,O-dimethylhydroxylamine to the triple C≡C bond. Similarly, the enaminone 37 was prepared in four steps from N-benzylxocarbonyl-L-threonine (33) (Scheme 5).
Scheme 5. (i) ClCOOBu, N-methylmorpholine, EtOAc, 0 °C, then MeNHOMe, 0 °C→r.t.; (ii) HC≡CMgBr, THF, –78 °C→r.t., then aq. NaHSO₄; (iii) Et₂NH, CH₂Cl₂, 0 °C→r.t.; (iv) HC≡CMgBr, THF, –78 °C→r.t., then aq. NH₄Cl; (v) Me₂C(OMe)₂, BF₃×Et₂O, r.t.; (vi) Mel, K₂CO₃, acetone, 0 °C→r.t.; (vii) i-PrMgBr, MeNHOMe, THF, –78 °C→–20 °C, then aq. NH₄Cl.

2.3.2 Synthesis of pyrazolo[1,5-α]pyrimidinyl substituted 2-phenylethylamines and β-amino alcohols

Enaminones 31a,b and 37 reacted with 3-aminopyrazole derivatives 38a–c as 1,3-dinucleophiles, to afford the corresponding (S)-1-(pyrazolo[1,5-α]pyrimidin-7-yl)-2-phenylethylamines 39a–e and (S)-1-amino-1-(pyrazolo[1,5-α]pyrimidin-7-yl)propan-2-ol (40) in 20–77% yields. In the reaction of 37 with 5-amino-1H-pyrazole-4-carbonitrile (38c), simultaneous removal of the ketal protecting group also took place (Scheme 6).³⁰
2.3.4 Synthesis of pyrazolyl substituted 2-phenylethylamines and β-amino alcohols

Acid-catalysed treatment of enamino ketones 31a,b with substituted hydrazines 3a,c,d,j,h–o, afforded the corresponding N-protected (S)-1-pyrazolyl-2-phenylethylamines 41a–k in 54–98% yields. Deprotection of compounds 41a,b,d,e,g,h,k by catalytic hydrogenation furnished free (S)-1-pyrazolyl-2-phenylethylamines 42a,b,d,e,g,h,k in 69–98% yields. In the same manner, L-threonine derived enamino ketone 32 was transformed with phenylhydrazine (3d) and 3-hydrazone-6-phenylpyridazine (3m) into compounds 34a and 34b, respectively. Deprotection by catalytic hydrogenation afforded (2S,3R)-1-amino-1-(1-H-pyrazol-5-yl)propan-2-ol (44a) and (2S,3R)-1-amino-1-[1-(6-phenylpyridazin-3-yl)-1H-pyrazol-5-yl]propan-2-ol (44b) (Scheme 7).�
3. Syntheses of functionalised pyrazoles from (1Z,4R*,5R*)-1-arylmethylidene-4-benzoylelamino-5-phenylpyrazolidin-3-one-1-azomethine imines

1,3-Dipolar cycloaddition reactions are useful methods for preparation of five-membered heterocycles. They enable access to polyfunctional compounds with multiple asymmetric centers, often with excellent stereocontrol.\(^{31}\) In contrast to well elaborated asymmetric cycloadditions in chiral nitrone, nitrile oxide, and azomethine ylide series,\(^ {32}\) much less examples of asymmetric cycloadditions to chiral azomethine imines have been reported.\(^ {33-37}\)
The importance of pyrazolidin-3-ones significantly rose in the last two decades, since several pyrazolidin-3-one derivatives exhibit biological activities and due to their applicability in industrial processes.\textsuperscript{9,10,38,39} For example, 2-acylamino-1-oxo-1\textsubscript{H},5\textsubscript{H}-pyrazolo[1,2-\textit{a}]pyrazole-7-carboxylates are useful scaffolds for preparation of conformationally constrained peptidomimetics.\textsuperscript{10,40} Since the first reports of Dorn\textsuperscript{41} and Oppolzer,\textsuperscript{42} 1,3-dipolar cycloaddition of stable, pyrazolidin-3-one derived, azomethine imines represent a simple and efficient method for preparation of 1\textsubscript{H},5\textsubscript{H}-pyrazolo[1,2-\textit{a}]pyrazol-1-ones. However, most of these studies were performed on achiral dipoles and on poorly substituted chiral azomethine imines.\textsuperscript{10,38–40,43,44} In connection with our studies in the field of 3-pyrazolidinones,\textsuperscript{34,45–50} we have previously reported regio- and stereoselective 1,3-dipolar cycloadditions to polysubstituted racemic (1\textsubscript{Z},4\textsubscript{R*},5\textsubscript{R*})-1-arylmethylidene-4-benzoylamino-5-phenylpyrazolidin-3-one-1-azomethine imines 47 leading to polysubstituted 1\textsubscript{H},5\textsubscript{H}-pyrazolo[1,2-\textit{a}]pyrazol-1-ones 48–50 (Scheme 8).\textsuperscript{34}

Scheme 8. (i) PhCHO, Ac\textsubscript{2}O, AcONa, 100 °C; (ii) N\textsubscript{2}H\textsubscript{4}×H\textsubscript{2}O (80%), reflux; (iii) ArCHO, EtOH, TFA (cat.), reflux; (iv) dimethyl acetylenedicarboxylate, anisole, reflux; (v) dimethyl maleate, anisole reflux; (vi) methyl or ethyl acetoacetate, MeOH, Et\textsubscript{3}N (1 equiv.), r.t.
Similarly, Chuang and Sharpless,\textsuperscript{36} as well as Husson, Bonin, Micouin, and coworkers,\textsuperscript{35,37} reported high facial selectivity of 1,3-dipolar cycloadditions to chiral azomethine imines, derived from pyrazolidinones and related 1,3,4-oxadiazinones.

On the other hand, our previous study on reactions of 1-arylmethylidene-5,5-dimethylpyrazolidin-3-on-1-azomethine imines with methyl propiolate showed, that the regioselectivity was strongly dependent on the \textit{ortho}-substituents at the aromatic ring.\textsuperscript{49} This results prompted us to investigate also the influence of \textit{ortho}-substituents in chiral azomethine imines \textsuperscript{47} on stereoselectivity and regioselectivity of cycloadditions.

\subsection*{3.1 Stereocontrol in cycloadditions to dimethyl maleate, dimethyl fumarate, methyl acrylate, and dimethyl acetylenedicarboxylate}

Azomethine imines \textsuperscript{47a–f} with the following aryl substituents attached to the exocyclic C=N double bond were chosen as the model 1,3-dipoles: phenyl (47a), 4-nitrophenyl (47b), 4-methoxyphenyl (47c), 3,4,5-trimethoxyphenyl (47d), 2,4,6-trimethylphenyl (47e), and 2,6-dichlorophenyl (47f). Cycloadditions were carried out with dimethyl maleate, dimethyl fumarate, and methyl acrylate as the model dipolarophiles. Cycloadditions of dipoles \textsuperscript{47a–f} to dimethyl maleate were all stereoselective, however, two diastereomeric types of cycloadducts were formed, depending on \textit{ortho}-substituents at the aromatic ring. \textit{ortho}-Unsubstituted dipoles \textsuperscript{47a–d} afforded the cycloadducts \textsuperscript{49a–d} with (2R*,3R*,5R*,6S*,7R*)-configuration, while \textit{ortho}-disubstituted azomethine imines \textsuperscript{47e,f} gave, stereoselectively, the major (2R*,3R*,5S*,6R*,7S*)-isomers \textsuperscript{49e,f}. In contrast, cycloaddition of \textit{ortho}-unsubstituted \textsuperscript{47a} to dimethyl fumarate (5) was not stereoselective and gave a mixture of \textsuperscript{51a} and three isomeric cycloadducts in a ratio of 33:30:22:15, which were separated by chromatography. On the other hand, reaction of dimethyl fumarate with \textit{ortho}-disubstituted \textsuperscript{47e} afforded the major (2R*,3R*,5S*,6R*,7R*)-isomer \textsuperscript{51e} in 68\% d.e.. Reactions of \textit{ortho}-unsubstituted \textsuperscript{47a,b,d} with methyl acrylate proceeded regioselectively and stereoselectively to give the (2R*,3R*,5R*,7R*)-isomers \textsuperscript{55a,b,d}, while cycloaddition of \textit{ortho}-disubstituted \textsuperscript{47e} was not selective and furnished a mixture of the major (2R*,3R*,5S*,6S*)-isomer \textsuperscript{52e} and three minor isomers in a ratio of 34:30:21:15, which were separated by chromatography (Scheme 9).\textsuperscript{51}
Scheme 9. (i) Anisole, reflux; (ii) chromatographic separation (CC followed by MPLC).

These results prompted us to reinvestigate the configuration of compounds, formed upon cycloaddition of dipoles 47a and 47f to dimethylacetylene dicarboxylate. Also in this case, stereocontrol was dependent on ortho-substituents. Thus, 47a gave cycloadduct 48a with \((2R^*,3R^*,5R^*)\)-configuration, while the ortho-disubstituted 48f gave cycloadduct 58f with the opposite sense of configuration at position 5 (Scheme 10).
Scheme 10. (i) Anisole, reflux.

Stereochemistry of these cycloadditions, which is apparently controlled by the stereodirecting phenyl group at position 3, as well as by the ortho-substituents at the aromatic ring, might be summarized in the following way:

(a) ortho-unsubstituted dipoles favoured formation of the major isomers with syn-oriented H–C(3) and H–C(5), while ortho-disubstituted dipoles favoured formation of the major isomers with anti-oriented H–C(3) and H–C(5),

(b) in all major isomers with a stereocenter at position 6, the H–C(5) and H–C(6) were always trans-oriented,

(c) cycloadditions to dimethyl maleate and dimethyl acetylenedicarboxylate were always stereoselective,

(d) cycloaddition to dimethyl fumarate was stereoselective only in the case of two ortho-substituents, and

(e) cycloadditions to methyl acrylate were selective only in the case of no ortho-substituents.

Possible explanation for different selectivity might be exemplified at best by cycloadditions of 47a–f to dimethyl maleate. Dipoles 47a–d with free ortho-positions in the aromatic ring can adopt the planar conformation 47'a–d allowing transition state for the concerted 1,3-dipolar cycloaddition. Formation of the compounds 49a–d could be explained by preferential endo-approach of dipolarophile from the less hindered face of the (1Z,4R*,5R*)-dipole. On the other hand, such planar conformation is not possible in the case of dipoles 47e,f with two ortho-substituents. Alternatively, stereoselective formation of 49e,f might be explained by a two-step 1,4-addition–cyclization mechanism. In the mesomeric structures 47'e,f, rotation around the N(1)–C(1') single bond gives the rotamers 47''e,f with the bulky aryl group twisted away from the phenyl ring at position 3. Conformers 47''e,f can undergo Michael-type anti-addition to the dipolarophile to form the intermediate zwitterions (or a biradicals),52 which cyclise into the final products 49e,f (Scheme 11).51
Scheme 11

Stereoselective formation of compounds 49e,f could also be in agreement with the exo-approach of the dipolarophile from the less hindered face of the (1E,4R*,5R*)-dipoles 47e,f.
However, this explanation does not seem suitable, since both, (Z)- and (E)-planar conformation of dipoles 47e,f would be sterically unfavourable due to two ortho-substituents and because Z/E-isomerization of dipoles 47e,f at 150 °C would consequently lead to a mixture of isomeric cycloadducts. In order to determine the possible Z/E-isomerisation, 1H NMR and NOESY spectra of azomethine imine 47f were recorded at 29, 62, 100, and 150 °C. Only one set of signals, observed in 1H NMR spectra even at 150 °C, was in agreement with retention of the (Z)-configuration. On the other hand, decreasing NOE between 1'–H and 5–H did not exclude the possibility of Z/E-isomerisation (Scheme 12).51

![Scheme 12](image)

### 3.2 Combinatorial synthesis of 5H-pyrazolo[1,2–a]pyrrolo[3,4–c]pyrazole-1,3,5(2H,3aH)-triones

In continuation, we focused our attention also on combinatorial studies. Since the reaction and isolation conditions for azomethine imines 47 are always the same (the dipoles precipitate from the reaction mixture), a series of azomethine imines 47 has recently been prepared by the parallel solution-phase approach and isolated simply by filtration, washing, and drying. In extention, the solution-phase approach was applied for the combinatorial synthesis of 15 tetrahydro-5H-pyrazolo[1,2–a]pyrrolo[3,4–c]pyrazole-1,3,5(2H,3aH)-triones 54a–o by reacting five azomethine imines 47a,b,d,e,f with three maleimides 53a–c. Maleimides were chosen, since they are also, like dimethyl maleate, the cisoid-dipolarophiles and cycloadditions were expected to proceed stereoselectively regardless of the ortho-substituents at the aromatic ring (c.f. Scheme 9). Upon heating in anisole followed by cooling, evaporation, trituration with ether, filtration, washing, and thorough drying, all products 54a–i and 54j–o were isolated in analytically pure form in 18–89% yields.53 According to expectations, two stereochemical types of cycloadducts, 54a–i and 54j–o, were formed, depending on ortho-substituents at the aromatic ring. Surprisingly, recent NMR and X-ray structural determinations showed, that the configurations at positions 6, 7 and 9 were in agreement with the previously established stereocontrol, while the configurations at positions 3a and 9a were not.51 This might be due to possible isomerisation at positions 3a and 9a in cycloadduct 54 or/and due to different steric demand of the dipolarophile 53 in comparison to dimethyl maleate (Scheme 13).53
Scheme 13. (i) maleimide 53a–c, anisole, reflux; (ii) evaporation, trituration with Et₂O, filtration, washing with Et₂O, drying \textit{in vacuo}.

### 3.3 Combinatorial studies on cycloadditions to β-keto esters.

Next, we investigated cycloadditions of azomethine imines 47 to β-keto esters 55,\(^{34}\) which result in the formation of two epimeric alkyl 3-aryl-6-benzoylamino-1-hydroxy-1-methyl-7-oxo-5-phenyltetrahydro-1H,5H-pyrazolo[1,2-\(\alpha\)]pyrazole-2-carboxylates, the major \((1S^*,2S^*,3R^*,5R^*,6R^*-)\)-isomers 50 and the minor \((1R^*,2S^*,3R^*,5R^*,6R^*-)\)-isomers 50’. During the preliminary studies it turned out, that \textit{ortho}-disubstituted dipoles 47e,f do not react.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Ar</th>
<th>R</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>54a</td>
<td>Ph</td>
<td>Ph</td>
<td>74</td>
</tr>
<tr>
<td>54b</td>
<td>4-nitrophenyl</td>
<td>Ph</td>
<td>84</td>
</tr>
<tr>
<td>54c</td>
<td>3,4,5-trimethoxyphenyl</td>
<td>Ph</td>
<td>75</td>
</tr>
<tr>
<td>54d</td>
<td>Ph</td>
<td>4-methylphenyl</td>
<td>48</td>
</tr>
<tr>
<td>54e</td>
<td>4-nitrophenyl</td>
<td>4-methylphenyl</td>
<td>57</td>
</tr>
<tr>
<td>54f</td>
<td>3,4,5-trimethoxyphenyl</td>
<td>4-methylphenyl</td>
<td>76</td>
</tr>
<tr>
<td>54g</td>
<td>Ph</td>
<td>Me</td>
<td>55</td>
</tr>
<tr>
<td>54h</td>
<td>4-nitrophenyl</td>
<td>Me</td>
<td>73</td>
</tr>
<tr>
<td>54i</td>
<td>3,4,5-trimethoxyphenyl</td>
<td>Me</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>54j</td>
<td>2,4,6-trimethylphenyl</td>
<td>Ph</td>
<td>63</td>
</tr>
<tr>
<td>54k</td>
<td>2,6-dichlorophenyl</td>
<td>Ph</td>
<td>82</td>
</tr>
<tr>
<td>54l</td>
<td>2,4,6-trimethylphenyl</td>
<td>4-methylphenyl</td>
<td>55</td>
</tr>
<tr>
<td>54m</td>
<td>2,6-dichlorophenyl</td>
<td>4-methylphenyl</td>
<td>89</td>
</tr>
<tr>
<td>54n</td>
<td>2,4,6-trimethylphenyl</td>
<td>Me</td>
<td>18</td>
</tr>
<tr>
<td>54o</td>
<td>2,6-dichlorophenyl</td>
<td>Me</td>
<td>84</td>
</tr>
</tbody>
</table>
Therefore, we have chosen three model *ortho*-unsubstituted azomethine imines 47a–c and one model *ortho*-monosubstituted azomethine imine 47g and nine model β-keto esters 55a–i for a combinatorial study on cycloaddition reactions. First, 12 reactions were carried out with ethyl (55a), benzyl (55b), and tert-butyl acetoacetate (55c). With exception of 50{47b; 55c}, the products were isolated as mixtures of epimers 50 and 50'. Phenyl (47a) and 4-nitrophenyl (47b) substituted dipoles reacted with all three acetoacetates 55a–c, while 4-methoxyphenyl (47c) and 2,4-dichlorophenyl substituted azomethine imine (47g) did not react in all cases. On the other hand, tert-butyl acetoacetate (55c) was the most reactive, since it underwent cycloadditions with all four azomethine imines 47a–c,g. (Scheme 14).53

\[
\begin{align*}
\text{Yield/D.e. (%)} & \quad 55a \quad 55b \quad 55c \\
\text{Ar (47) } & \text{Et} \quad \text{Bn} \quad t\text{-Bu} \\
\text{47a phenyl} & 76/48 \quad - \quad 78/46 \\
\text{47b 4-nitrophenyl} & 75/62 \quad 89/60 \quad 86/100 \\
\text{47c 4-methoxyphenyl} & n.c. \quad 34/16 \quad 80/68 \\
\text{47g 2,4-dichlorophenyl} & n.c. \quad n.c. \quad 66/64 \\
\end{align*}
\]

(*n.c.*) No conversion detected by TLC.

**Scheme 14.** (i) MeOH, Et₃N (1 equiv.), r.t.

Finally, 24 cycloadditions were performed with dipoles 47a–c,g and β-keto esters 55d–i with variable substituents at the β-position (55d (R = Et), 55e (R = n-Pr), 55f (R = i-Rr), 55g (R = t-Bu), 55h (R = Ph), and 55i (R = CH₂COOMe). In contrast to cycloadditions to alkyl acetoacetates 55a–c, isomerically pure cycloadducts were isolated upon reactions of 47a–c,g with β-keto esters 55d–i. An exception was compound 50/50' {47a; 55d}, which was obtained in 72% d.e. 4-Nitrophenyl substituted azomethine imine 47b was again the most reactive and gave cycloadducts also with sterically more demanding keto esters 55g–i (R = t-Bu, Ph, CH₂COOMe), while the other three dipoles 47a,c,g reacted only with sterically less demanding keto esters 55d–f (R = Et, n-Pr, i-Rr). These results also support the indication, that, besides steric factors, the
electronic effects should also be taken into account by planning a combinatorial synthesis of pyrazolo[1,2-a]pyrazolone type of peptidomimetics (Scheme 15).\(^{53}\)

\[
\begin{align*}
\text{Scheme 15. (i) MeOH, Et}_3\text{N (1 equiv.), r.t.}
\end{align*}
\]

**Acknowledgements**

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References and Notes


