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Asymmetric 1,3-dipolar cycloadditions of a chiral nonracemic glyoxylic azomethine imine

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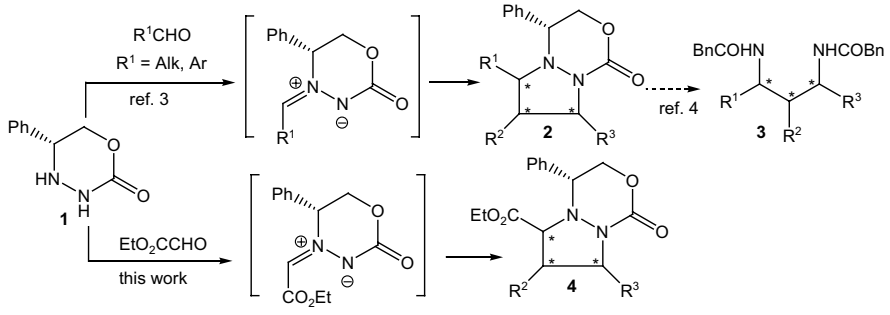
Abstract—The reactivity of a chiral nonracemic glyoxylic azomethine imine has been investigated. This species reacts with a wide range of dipolarophiles, with a complete regio- and facial stereoselectivity. The introduction of an electron-withdrawing substituent on the ylide leads to a lower *endo* selectivity with electron-withdrawing dipolarophiles, but to an improved *exo* selectivity with styrene derivatives when compared to the reactivity of aliphatic- or aromatic-substituted ylides.

1,3-Dipolar cycloadditions are reactions of considerable interest in diversity-oriented synthesis (DOS),[1] since they can provide access to polyfunctional molecules with overall good control of the relative configuration of several consecutive asymmetric centres, under relatively simple and scalable experimental procedures.[2] In a series of papers, we have reported that chiral nonracemic cyclic hydrazine **1** reacts with aliphatic or aromatic aldehydes, generating azomethine imine ylides capable of undergoing highly regio- and stereoselective cycloaddition with a wide range of olefins, and delivering polyfunctional pyrazolidines **2** in good yield (Scheme 1).[3] We have also demonstrated that polyfunctional 1,3 diamines could be obtained from these intermediates in a short synthetic sequence.[4]

We now report in this paper the results of our investigations into the formation and reactivity of the ylide



Scheme 1.

Keywords: Cycloadditions; Azomethine imine; Asymmetric synthesis.
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derived from the condensation of hydrazine **1** with ethyl glyoxylate (Scheme 1).

While the use of aromatic and, in a lesser extent, aliphatic aldehydes is well documented for the generation of azomethine ylides, reports on the preparation and reactivity of ylides resulting from a condensation with alkylglyoxylates are scarce.[5] Works of the Harwood's group have shown that good selectivity could be achieved in some cases, despite a lower reactivity of the ylide.[5d]

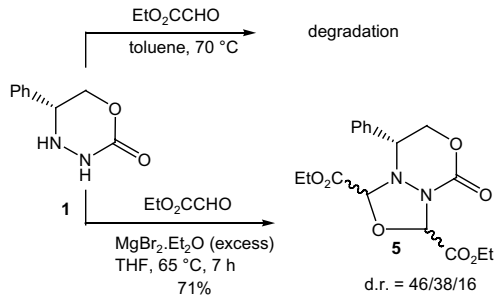
A more contrasted behaviour has been reported by the group of Grigg[5c] and Risch and co-workers.[5f] In both cases, only electron poor olefins were used as standard dipolarophiles. On the contrary, good results have been described with achiral azomethine imines by Khau and Martinelli.[5e]

First attempts to perform the cycloaddition under standard conditions proved to be unsuccessful, leading mainly to starting material or degradation.[6] We then tried to prepare oxadiazolidine **5**, in order to generate the reactive ylide by a cycloreversion process. While thermal or protic activation failed, we were pleased to see that a diastereomeric mixture of **5** could be obtained in good yield in the presence of magnesium bromide etherate (Scheme 2).[7]

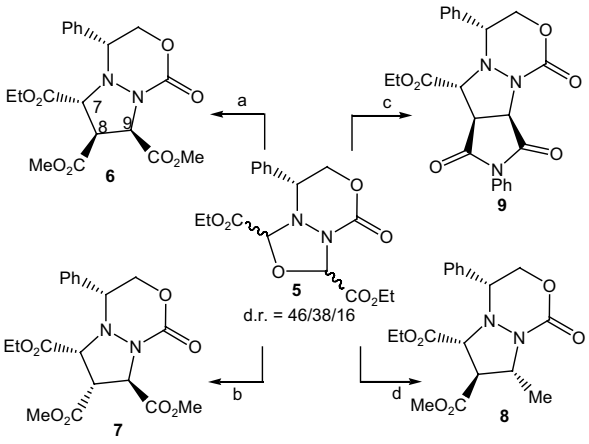
The tandem cycloreversion–cycloaddition was then investigated in the presence of various electron poor dipolarophiles, leading to cycloadducts **6**–**9** in 71–83% yield (Scheme 3).

While the *endo* selectivity was usually excellent with ylides generated from aliphatic or aromatic aldehydes, a lower selectivity was observed in the glyoxylic series. The approach of dimethylmaleate proved to be mostly *endo*, as depicted by crystal structure X-ray analysis of compound **6** (Fig. 1),[8] whereas the use of dimethylfumarate led to the *exo* adduct **7** as a major diastereomer. In all the cases, the facial selectivity was excellent, leading to a single epimer at the C7-position (Scheme 3), as a result of a dipolarophile approach from the less sterically hindered face of a S-shape ylide.

This loss of *endo* selectivity is not unexpected, since the lowering of the HOMO level of the dipole by an electron-withdrawing group should lead to a lower $HOMO_{dipole}$–$LUMO_{dipolarophile}$ control.[9] This hypothesis was confirmed by cycloadditions with styrene derivatives (Scheme 4).



Scheme 2.



Scheme 3. Reagents and conditions: (a) dimethyl maleate (3 equiv), toluene, 80 °C, 8 days, 84%, de=70%; (b) dimethyl fumarate (3 equiv), toluene, 80 °C, 7 days, 71%, de=32%; (c) *N*-phenyl maleimide (4 equiv), toluene, 3 days, 80 °C, 73%, de=49%; (d) methyl crotonate (4 equiv), toluene, 11 days, 80 °C, 71%, de=18%.

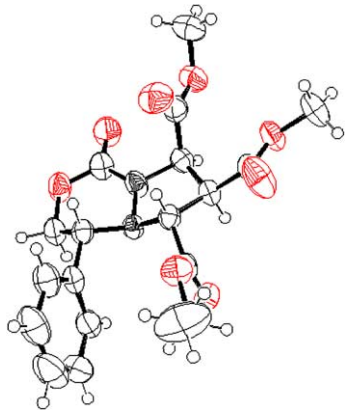
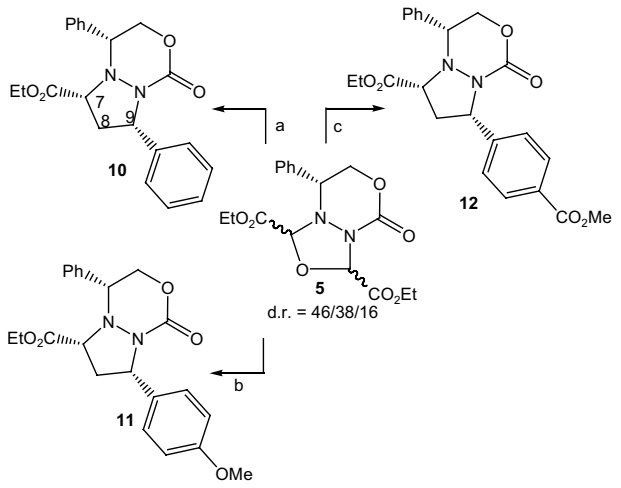


Figure 1. ORTEP diagram of compound **6**.

With electron rich olefins, cycloadducts **10**–**12** could be obtained in 48–65% yield, with diastereoselectivities greater than 85%. In all cases, the reaction was completely regioselective and led to the *exo* adduct as a major diastereomer. This stereoselectivity enhancement, when compared to the results obtained with ylides prepared from aliphatic or aromatic aldehydes, as well as the regioselective formation of C7, C9 *cis* substituted compounds, is typical for a $LUMO_{dipole}$–$HOMO_{dipolarophile}$ controlled condensation, which can be expected with ylides bearing an electron-withdrawing substituent. These results are noteworthy, since they enable a formal access to diamino substrates having an ester and an aromatic substituent in a 1,3 arrangement, whereas the use of aromatic aldehydes and unsaturated esters should deliver diamines with these two functionalities in a 1,2-position.



Scheme 4. Reagents and conditions: (a) styrene (10 equiv), toluene, 7 days, 75 °C, 48%, de=90%; (b) 4-vinylanisole (8 equiv), toluene, 12 days, 70 °C, 51%, de=94%; (c) 4-vinyl-methylbenzoate (8 equiv), toluene, 12 days, 70 °C, 65%, de=85%.

In conclusion, the ylide derived from the condensation of hydrazine **1** with ethyl glyoxylate can be generated by a cycloreversion reaction, and reacts with a wide range of dipolarophiles.[10] The regio- and facial selectivity of the cycloadditions are perfectly controlled in all of the cases. When compared to the alkyl- or aromatic series, the glyoxylic ylide led to a lower *endo* selectivity with dipolarophiles bearing electron-withdrawing groups, but to an improved *exo* selectivity with styrene derivatives. These results broaden the scope of this three-component asymmetric condensation, and increase the molecular diversity that can be generated with this reaction.

Acknowledgements

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6. A 50% commercial toluene solution of ethylglyoxylate was used in all experiments. ^{1}H NMR of this solution (the high concentration of the reagent enables the direct NMR of the solution *without the use of a deuterated solvent*) shows that this aldehyde exists mainly as a trimeric form, and that the proportion of free aldehyde can be roughly estimated to 10%.
7. Although the use of Lewis acid has been described to have an effect on dipolar cycloadditions, the role of magnesium bromide etherate in our case is not completely clear. It can improve the reactivity of the aldehyde in the cycloaddition, but also catalyze the deoligomerization of this reagent. For the use of $MgBr_2{\cdot}Et_2O$ in dipolar cycloadditions, see: Harwood, L. M.; Manage, A. C.; Robin, S.; Hopes, S. F. G.; Watkin, D. J.; Williams, C. E. *Synlett* **1997**, 777–780.
8. Crystal data for **6**: formula $C_{19}H_{22}N_2O_8$, orthorhombic, space group $P2_12_12_1$; $a = 7.936(2)$, $b = 10.650(2)$, $c = 23.818(4)$ Å, $V = 2013.1(7)$ Å^3, $Z = 4$, $M = 406.4$ g, $D_c = 1.341$ g cm^{-3}; $F(000) = 856$. The structure was solved by direct methods using SHELXS-97. Refinement, based on F^2, was carried out by full matrix least squares with SHELXL-97 software. An ORTEP diagram is given in the figure. Non-hydrogen atoms were refined anisotropically. The hydrogen atoms were positioned geometrically and refined riding on their carrier atom with isotropic thermal displacement parameters fixed at 1.2 times those of their parent atoms. Convergence was reached at $R1 = 0.040$ for 2153 reflections ($I > 2\sigma(I)$), $wR2 = 0.143$ for all data and $S = 0.918$ for 265 parameters. The residual electron density in the final difference Fourier does not show any feature above 0.156 e Å^{-3} and below −0.189 e Å^{-3}. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 225965 copies 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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10. Experimental procedure. The preparation of **6** is typical: carbazate **1** (see Ref. 3 for the preparation of **1**) (75 mg, 0.42 mmol), ethylglyoxylate (50% in toluene, 333 μL, 4 equiv) and $MgBr_2{\cdot}Et_2O$ (210 μL) were dissolved in THF (5 mL) and stirred at 65 °C for 7 h. The crude reaction mixture was concentrated, and purified by flash chromatography on silica gel (EtOAc–cyclohexane=3:7) to give oxadiazolidine **5** as a mixture of three diastereomers (110 mg, 71%). A diastereomeric mixture of **5** (70 mg, 0.19 mmol) and dimethylmaleate (72 μL, 3 equiv) were dissolved in toluene (2 mL) and stirred at 80 °C for 8 days. The reaction mixture was concentrated, and the de of the crude was determined by NMR (de=70%). Purification by flash chromatography on silica gel (EtOAc–cyclohexane=3:7) gave one fraction (55 mg, 71%) of diastereomerically pure pyrazolidine **6** and a second fraction (10 mg) of a diastereomeric mixture of **6** (global yield: 84%). Pyrazolidine **6**: white crystals, mp (Et_2O)=130–132 °C; $[\alpha]_D$ −155° (*c* 0.98, $CHCl_3$). ^{1}H NMR (300 MHz): δ 7.40 (m,

5H), 4.90 (d, $J = 8.7$ Hz, 1H), 4.45 (dd, $J = 10.9$, 10.7 Hz, 1H), 4.15 (dd, $J = 11.2$, 3.1 Hz, 1H), 4.09 (dd, $J = 10.5$, 3.1 Hz, 1H), 4.09 (d, $J = 11.2$ Hz, 1H), 3.85 (dd, $J = 11.2$, 8.7 Hz, 1H), 3.80 (s, 3H), 3.75 (m, 1H), 3.68 (s, 3H), 3.27 (dq, $J = 10.7$, 7.1 Hz, 1H), 0.9 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (75.43 MHz): δ 169.6, 168.3, 167.1, 149.1, 132.3, 128.9–129.7, 72.2, 67.4, 65.5, 61.7, 59.7, 53.0, 52.7, 49.2, 13.5. MS (CI): 407 (MH^+). IR (cm^{-1}): 1747, 1700. Elemental analysis. Calcd: C, 56.15; H, 5.46; N, 6.89. Found: C, 56.04; H, 5.49; N, 6.92.