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# A novel reaction cascade leading to a spontaneous intramolecular dipolar cycloaddition through simultaneous generation of 1,3-dipole and dipolarophile

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## ARTICLE INFO

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### ABSTRACT

Ornithine methyl ester reacts with aromatic aldehydes to generate bis-Schiff bases, which depending on the structure of the aromatic aldehyde, further undergo an intramolecular cycloaddition through the transient formation of a reactive 1,3-dipole.

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Dipolar cycloadditions belong to an important class of reactions extensively employed in the synthesis of complex molecules.<sup>1</sup> The ability to create multiple stereo centers in a defined way is definitely a major reason for their utility. Similarly tandem/cascade synthesis<sup>2</sup> creates often in a few steps a complex molecular architecture in a simple, predictable way. We report herein examples combining these two concepts to engender bicyclic systems in appropriately substituted molecules.

L-Ornithine methyl ester hydrochloride (**I**) reacts at room temp with 2 equiv of *p*-chlorobenzaldehyde to form the expected bis-Schiff base (**II-f**) as the only product without any apparent racemization of the bis-Schiff base. On the other hand a bicyclic structure (**IV-a**) results (with three stereo centers) as a single diasteromer (racemic) as the sole isolable product in the case of *p*-nitrobenzaldehyde (Scheme 1). The corresponding bis-Schiff base (**II-a**) does not survive under these conditions.

We rationalize the outcome of these reactions as outlined in Scheme 2. In the case of *p*-nitrobenzaldehyde, the initially formed bis-Schiff base, generates a 1,3-dipole in a fast step which further undergoes a rapid intramolecular cycloaddition with a favorably positioned imino dipolarophile for cycloaddition. Ostensibly the *p*-nitro group enhances the acidity of the alpha-hydrogen (Scheme 2) and stabilizes the 1,3-dipole formed. The 1,3-dipole



Scheme 1. Reaction of L-ornithine methyl ester dihydrochloride with aromatic aldehydes.





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III. Proposed reactive conformation

Scheme 2. Bicyclic heterocycle formation through an intramolecular 1,3-dipolar addition.

Table 1Influence of Ar in ArCHO on the dipolar cycloaddition  $\underline{I} + 2Ar$ -CHO $\rightarrow$ Bis-Schiff Base ( $\underline{II}$ ) + Bicyclic Hetrocycle ( $\underline{IV}$ )

Sl.no.	Ar in ArCHO	II <sup>a,b</sup>	IV <sup>a</sup>	Sl.no.	Ar in ArCHO	II <sup>a,b</sup>	<b>IV</b> <sup>a</sup>
a	4-Nitrophenyl-	0	100	f	4-Chlorophenyl	100 <sup>d</sup>	0
b	2-Nitrophenyl-	0	100 <sup>c</sup>	g	2,3 Dichlorophenyl-	85	15
с	3-Nitrophenyl-	92	8	ĥ	3,4 Dichlorophenyl-	100	0
d	4-Pyridyl-	0	100	i	2,6 Dichlorophenyl-	100 <sup>e</sup>	0
e	2-Chlorophenyl-	90	10 <sup>c</sup>	j	Phenyl-	100	0

<sup>a</sup> The relative ratios of **II** and **IV** are estimated from the NMR integrations of the crude product.

<sup>b</sup> NMRs of all the bis-Schiff bases reported herein indicate a single isomer only; *anti-geometry at both imino groups*.

<sup>c</sup> Specific rotations were measured to be essentially zero for both these products { $[\alpha]_D 0^\circ$  for IV-b and  $[\alpha]_D 0.8$  for IV-e, 2% in CHCl<sub>3</sub>}.

 $^d$  For II-f,  $[\alpha]_D$   $-100.6^\circ\!.$ 

<sup>e</sup> For **II-i**, [α]<sub>D</sub> 29.4°.

assumes a distortionless conformation stabilized and held in position in a reactive conformation by the intramolecular H-bonding as shown.<sup>3</sup> Further the endo-type transition state and aryl-aryl stacking interactions may further favor this transition state. Racemization occurs on formation of the 1,3-dipole and the bicyclic heterocycle is isolated as a racemic product (all bicyclic heterocycles reported in this Letter are isolated as racemic compounds).

This is an interesting case of an intramolecular dipolar cycloaddition<sup>4</sup> wherein the partners of the cycloaddition, namely, the 1,3dipole and the dipolarophile are both generated in the same flask simultaneously and in situ undergo further cycloaddition. The imino group is also an uncommon dipolarophile.

In the other case (see Scheme 1) involving *p*-chlorobenzaldehyde, the *p*-chloro substituent does not enhance the acidity of the alpha-hydrogen enough to lead to the 1,3-dipole leaving the bis-Schiff base as the end product. The inertia toward dipole formation is further indicated by the preservation of enantiomeric purity of the bis-Schiff base evidenced by unchanged optical rotation of this bis-Schiff base (**IIf**) on prolonged continuous stirring under the reaction conditions (see Table 1). Once the 1,3-dipolar structure forms, reversion back to the starting Schiff base or progress toward the product, namely **IV**, will result in racemization.

The mechanism derives impressive support from the observation that *o*-nitrobenzaldehyde reacts with L-Ornithine methyl ester hydrochloride (I) under the reaction conditions readily to form exclusively the bicyclic structure (1,3-dipole formation) facilitated by the *o*-nitro substitutent through enhanced acidity<sup>5</sup> of the alpha-hydrogen, (see Scheme 2) whereas the reaction halts at bis-Schiff base stage for *m*-nitrobenzaldehyde (Scheme 3). This is expected since the *o*-nitro substituent will increase the acidity of the alpha-hydrogen greatly whereas *m*-nitro does not exercise the same influence on the acidity.

The structures of the bicyclic heterocycles are derived from NMR and supported by the X-ray structure<sup>6</sup> for **IV-b**. The X-ray structure of **IV-b** (Fig. 1) shows some interesting features. The nitro groups are forced away from the carboxymethyl group presumably by dipole–dipole repulsions. The *cis* orientation of the two *o*-nitrophenyl rings is confirmed by the torsion angle (in degrees) about the C(2)–C(3) bond: C(8)–C(2)–C(3)–C(17) = 38.1° (Fig. 1). The nitro substituent on each of the phenyl rings is not coplanar with the respective phenyl rings. Even though the X-ray structure was obtained for only one analog, namely **IV-b**, from the similarity of the NMR spectra in particular the near identity of the coupling constants ( $J_{H2-H3} \sim 6.6$  Hz), it is concluded that the stereochemistry of all bicyclic compounds **IV** is the same.

We probed the reaction further by influencing the acidity of the alpha-hydrogen (see Scheme 2). Using pyridine-4-carboxaldehyde, the bicylclic product (**IVd**) is the sole one formed. It is well known that the pyridine structure stabilizes carbanionic character at attached carbons at C-2 and C-4 positions.<sup>7,8</sup>

Next we examined a series of chloro substituted benzaldehydes to modulate the acidity of the alpha-hydrogen inductively. Orthochlorine substituent induces some propensity toward bicyclic



Scheme 3. Bicyclic heterocycle formation through intramolecular 1,3-dipoar addition.



Figure 1. X-ray structure of IV-b.

heterocycle formation. Distant halogen substitution on the aryl ring of the reaction partner aromatic aldehyde (at meta and para positions) results in exclusive bis-Schiff base formation not eager to react further (see Table 1).

Interestingly when 2,6-dichlorobenzaldehyde was used, no bicylclic product resulted. Only the bis-Schiff base (**IIi**) was formed as a nice solid. Prolonged stirring under the reaction conditions resulted in neither the formation of the corresponding bicyclic heterocycle nor the racemization of the bis-Schiff base (**IIi**) thus showing its resistance to form the 1,3-dipole. In this case, the 1,3-dipole stabilization (and for the requisite acidity of the alpha-hydrogen as a precedent) would compel coplanarity of the 2,6-dichlorophenyl group with the 1,3-dipole plane. When the 2 and

6 positions of the phenyl group are both occupied by a chlorine atom (van der walls radius  $\sim$ 1.8 Å), such a coplanar structure is rendered very unfavorable.

In summary, a novel intramolecular 1,3-dipolar cycloaddition (wherein both the 1,3-dipole and the dipolarophile are both contemporaneously generated) occurring at rt under mild conditions has been demonstrated with structural influences on the mechanism of cycloaddition.<sup>9</sup> The recently reported<sup>10</sup> asymmetric variations of 1,3-dipolar cycloaddition, especially using chiral catalysis, provide further impetus to explore this reaction along such lines. Chiral forms of the bi-proline structures of **IV** offer interesting possibilities in iminium ion chemistry.

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#### Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013. 07.009. These data include MOL files and InChiKeys of the most important compounds described in this article.

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- 6. Crystal data for **IV-b**: a = 11.6597(4) Å, b = 7.5080(2) Å, c = 22.9561 (6) Å,  $\alpha = 90^{\circ}$  $\beta = 100.664(2)^{\circ}$   $\gamma = 90^{\circ}$  V = 1974.89(10) Å<sup>3</sup>, Z = 4, and space group P21/c (No. 14). Crystallographic data (excluding structure factors) for **IV-b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 714913. 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 email: deposit@ccdc.cam.ac.uk).
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- 8. Use of pyridoxal in the place of pyridine-4-carboxaldehyde gave a complex mixture of products.
- 9 Experimental: Following is the procedure for IV-b, but is representative for all the other bicyclic heterocycles (IV-a, IV-d, IV-e, and IV-g). In a RB flask equipped with a magnetic stirrer, L-ornithine methyl ester dihydrochloride (I, 5.0 g, 22.9 mmol) and 2-Nitrobenzaldehyde (7.5 g, 49.7 mmol) were taken in methylene chloride (70 ml). The suspension was stirred at 0 °C and after 15 min, triethylamine (4.6 g, 46 mmol) in 10 ml of methylene chloride was added slowly. The reaction mixture was allowed to warm to rt and stirred overnight. The reaction mixture was diluted with methylene chloride, washed with water, dried over Na2SO4, and the solvent was evaporated to give the crude product (the relative ratios of bis-Schiff bases to cyclized heterocycle were deduced from the NMR spectra at this stage). The crude product IV was purified by column chromatography on silica gel using hexane-ethyl acetate as eluent. Isolated yield: 5.6 g (60%); mp 126–128 °C;  $C_{20}H_{20}N_4O_6$  Calcd C, 58.24, H, 4.89, N, 13.58; Found: C, 58.00; H, 4.75; N, 13.54; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) 1.98 (1H, m); 2.10 (2H, m); 2.38 (1H, m); 3.13 (1H, m); 3.23 (1H, br s); 3.46 (1H, m); 3.89 (3H, s); 5.32, and 5.34 (2H, ABq, J = 6.60 Hz); 6.91 (1H,dd, J = 1.47, 8.06 Hz); 7.18 (1H,dt, J = 1.47, 7.33 Hz); 7.23–7.28 (2H,m); 7.49–7.53 (2H,m); 7.72-7.80 (2H,m); <sup>13</sup>C NMR (125 MHz) 174.91, 149.45, 148.53, 134.60, 132.33, 131.80, 131.66, 130.66, 128.78, 128.27, 127.74, 124.54, 123.81, 89.31, 69.53, 58.78, 56.02, 52.80, 37.48, 25.01;

*Bis-Schiff bases*: The following procedure for **II-f,i,j** is exemplary. Schiff bases **IIg**, **h** were not isolated in a state of purity. In a clean dry flask containing methylene chloride (600 ml), *p*-chlorobenzaldehyde (77.0 g, 548 mmol) was added followed by L-ornithine methyl ester dihydrochloride(I) (60.0 g, 274 mmol). The flask was cooled to  $0-5^{\circ}$ C and triethyl amine (63.0 g, 617 mmol) was added over a period of 3-4 h keeping the temp below  $10^{\circ}$ C. At the end of the addition, the reaction was allowed to warm upto rt and stirring was continued for 15 h. The precipitated TEA-HCl was filtered and the organic layer was washed with water and dried over sodium sulfate. Methylene chloride was removed under vacuum and hexane (500 ml) was added to the resulting thick liquid to induce crystallization. The product was filtered and dried under vacuum. Yield 80.0 g (75%). mp:  $92-94^{\circ}$ C;  $C_{20}H_{20}Cl_2N_2O_2$  Calcd

C:61.39, H:5.15, N:7.16; Found: C:61.16, H:4.98, N:7.26; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) 1.63–1.76 (2H, m); 1.99 (1H, m), 2.09 (1H,m); 3.63 (2H, t, J = 6.84 Hz); 3.75 (3H, s); 4.04 (1H, dd, J = 4.88, 8.79 Hz); 7.37 (2H, d, J = 7.81 Hz); 7.39 (2H, d, J = 7.81 Hz); 7.39 (2H, d, J = 7.81 Hz); 7.71 (2H, d, J = 7.81 Hz); 8.22 (1H, s); 8.25 (1H, s). The bis-Schiff bases were not stable toward chromatography on silica gel. The NMR of all the bis-Schiff bases disclosed in this letter showed a single isomer only (*syn-anti* isomers about the two imine bonds; presumably only *anti-anti* isomer exists both in solid and solution states)

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