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## **1,3-Dipolar Cycloaddition Reactions with Azomethine Ylides Catalysed by Ag(I). Synthesis of Substituted Prolines**

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**Abstract:** The study of the stereochemistry of substituted prolines, synthesised by 1,3-dipolar cycloaddition reactions between azomethine ylides and alkenes employing substoichiometric amounts of Ag(I) is reported here

**Keywords:** Cycloaddition, Ag(I) catalysis, Azomethine ylides, Proline.

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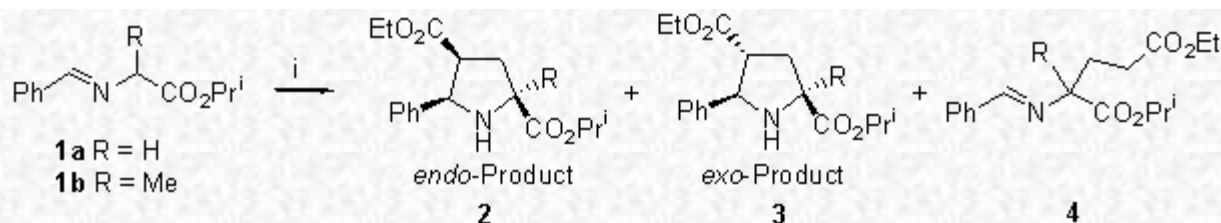
### **Introduction**

1,3-Dipolar cycloaddition reactions are one of the best and more widely used methods for the construction of five-membered ring in a convergent and stereocontrolled manner[1]. When azomethine ylides and alkenes are the two components of this cycloaddition reaction prolines are diastereoselectively obtained in good yield. The importance of substituted prolines in catalysis, pharmacology or biology is well recognised[2]. In this communication we will describe the influence of using substoichiometric amounts of Ag(I)[3], in the title 1,3-dipolar cycloaddition reaction, determining the optimal reaction conditions required for the diastereoselective preparation of substituted prolines.

### **Discussion**

Iminoesters **1a,b**, bearing an isopropyl group at the ester moiety, are resistant to basic media at room temperature and reacted with ethyl acrylate in the presence of metal salts at this temperature. Owing to this cycloaddition reaction is sensitive to many factors, it has been studied the influence of the R nature and solvent, base and additive effects. The results of this survey showed that Ag(I) cations are the best Lewis acid in order to achieve better diastereoselectivities and chemical yields. Other salts like Li(I), Zn(II), Co(II), Mg(II), Sn(IV), Ti(IV), Tl(I) with different counteranions were also tested. Usually amines or even stronger bases like DBU or tetramethylguanidine are employed, however this reaction can be run in the presence of cheaper bases such as NaOH and KOH. The latter one proved to be more reactive giving cycloadducts **2** in good yield (Scheme and Table). The solvent was also important[2] thus, from all tested solvents toluene and THF/tetrabutylammonium chloride (TBAC) afforded the best results of cycloadduct **2**.

As it is depicted in the Table this method is faster and more stereoselective than the thermal one, also yields are higher at room temperature avoiding decomposition or polymerisation products, which are detected in the reaction run in refluxing toluene (entries 1-3 and 4-6). The reaction with toluene at room temperature is slower than the analogous with THF/ammonium salt but the *endo*-diastereoselectivity is slightly higher affording similar yields (entries 2,3 and 5,6). By other side, glycine derivative **1a** reacts faster than alanine one **1b** (entries 2,4 and 3,4) which confirm the importance of steric effect in this reaction.[4].



**Reagents:** i. Ethyl acrylate, AgOAc (10 mol%), KOH (10 mol%), solvent (see Table).

**Table**

Entry	Dipole	Solvent	T(°C)	t <sub>r</sub> (h)	Product Ratio 2 : 3 : 4	Yield(%) <sup>a</sup>
1	<b>1a</b>	Toluene	110 <sup>b</sup>	19	84 : 7 : 1 <sup>c</sup>	91
2	<b>1a</b>	Toluene	25	12	96 : 4 : 0	95
3	<b>1a</b>	THF <sup>d</sup>	25	7	95 : 3 : 2	93
4	<b>1b</b>	Toluene	110 <sup>b</sup>	19	---- <sup>e</sup>	89
5	<b>1b</b>	Toluene	25	5	100 : 0 : 0	92
6	<b>1b</b>	THF <sup>d</sup>	25	1	93 : 7 : 0	92

<sup>a</sup> Isolated yield. <sup>b</sup> Sealed tube. <sup>c</sup> Remaining 8% are decomposition products. <sup>d</sup> TBAC (5 mol%) was used. <sup>e</sup> Other diastereomers were detected together with compounds **2**, **3** and **4**.

## Conclusion

1,3-Dipolar cycloaddition reaction between stabilised azomethine ylides and electrophilic olefins can be performed, diastereoselectively and in good yields, in the presence of substoichiometric amounts of both Ag(I) and inorganic bases.

## Experimental Part

The full experimental section will be described elsewhere. General procedure for the 1,3-dipolar cycloaddition reaction of iminoester **1b** and ethyl acrylate (entry 6) follows:

To a solution of iminoester **1b** (55 mg, 0.25 mmol) and ethyl acrylate (33 mL, 0.3 mmol) in THF (3 mL) was added, in this order, silver acetate (4.2 mg, 0.025 mmol), TBAC (4 mg, 0.0125) and potassium hydroxide (1.4 mg, 0.025 mmol) and the resulting mixture was stirred for 1h. The solvent was evaporated under vacuo and ethyl acetate (5 mL) added. This suspension was percolated through a silica-gel path and the solvent evaporated under vacuo affording compound **2** as major product (77 mg, 92%) as a colourless liquid.

IR (KBr): 3363, 1731 cm<sup>-1</sup>.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): 0.73 (t, *J* = 7.3 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>); 1.23 [d, *J* = 6.0 Hz, 6H, CH(CH<sub>3</sub>)<sub>2</sub>]; 1.41 (s, 3H, NCCH<sub>3</sub>); 1.97 (dd, *J* = 13.4 and 7.9 Hz, 1H, NCCH<sub>2</sub>); 2.60 (dd, *J* = 13.4 and 6.0 Hz, 1H, NCCH<sub>2</sub>); 3.10 (br s, 1H, NH); 3.25 (dd, *J* = 7.9 and 7.3 Hz, 1H, CHCO); 3.59 (m, 2H, CH<sub>2</sub>O); 4.75 (d, *J* = 7.3 Hz, CHPh); 5.06 [sep, *J* = 6.1 Hz, 1H, CH(CH<sub>3</sub>)<sub>2</sub>]; 7.10-7.25 (m, 5H, ArH).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): 13.59 (CH<sub>3</sub>CH<sub>2</sub>), 21.65, 21.68 [(CH<sub>3</sub>)<sub>2</sub>CH], 27.50 (CH<sub>3</sub>CN), 40.38 (CH<sub>2</sub>CN), 50.45 (CHCO), 60.08 (CH<sub>2</sub>O), 65.01 (CPh), 65.59 (NCCH<sub>3</sub>), 68.63 [CH(CH<sub>3</sub>)<sub>2</sub>], 126.03, 127.08, 128.20, 139.19 (ArC), 172.51 and 175.4 (2xCO).

MS (EI): 320 (M<sup>+</sup>+1, 0.4%), 276 (M<sup>+</sup>-43, 0.2) and 232 (100).

## References and Notes

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