

Figure 1. Titanium Mediated Chelation Transition State.

ed aldol condensation of the silyl ketene acetal derived from *N*-methyl ephedrine-*O*-propionate, in which the ephedrine nitrogen was expected to bind to titanium metal in the transition state.

In summary, we found that the silyl ketene acetal of *S*-2-pyridyl thioester condensed with several aldehydes to give highly *syn* selective aldol products irrespective of its geometry. The selectivity could be explained in terms of chelation model. The 2-mercaptopyridyl moiety of the aldol adduct is a good leaving group, thus it would be utilized in further synthetic transformation according to the conventional methods.

## Experimental Section

**Typical procedure for the aldol condensation.** To a cooled ( $-78\text{ }^{\circ}\text{C}$ ) solution of 282 mg (1.0 mmol) of the silyl ketene acetal **1** and 83  $\mu\text{L}$  (1.1 mmol) of cyclopropane carboxaldehyde in 10 mL of dichloromethane was added dropwise 1.1 mL (1.1 mmol) of titanium (IV) chloride in 1.0 M dichloromethane, and the red solution was stirred for 0.5 h at  $-78\text{ }^{\circ}\text{C}$ . Warmed to  $0\text{ }^{\circ}\text{C}$  over 0.5 h, the mixture was further stirred for 1.0 h at  $0\text{ }^{\circ}\text{C}$  and then quenched with saturated sodium bicarbonate solution. The precipitate was filtered off, and the organic phase was separated, dried over magnesium sulfate, and concentrated to afford a yellow oil, which was purified by flash chromatography (hexane : ethyl ether = 1 : 1) to give 199 mg (84%) of product as a pale yellow oil.

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- For example, thioesters can be easily converted to acids ( $\text{Hg}^{2+}$ ,  $\text{H}_2\text{O}$ ), esters ( $\text{Hg}^{2+}$  or  $\text{Tl}^{3+}$ , alcohol), alcohols (LAH,  $\text{H}_2/\text{Ra-Ni}$ , or  $\text{Ni}_2\text{B}$ ), aldehydes ( $\text{H}_2/\text{Ra-Ni}$ ), ketones (RM) and so on.
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- In Lewis acid mediated aldol condensation, highly *syn* selective products were reported in case of a few excep-

tional cases; (a) From asymmetric aldol reaction using chiral tin (II) catalysts, Kobayashi, S.; Uchiro, H.; Fujishita, Y.; Shiina, I.; Mukaiyama, T. *J. Am. Chem. Soc.* **1991**, *113*, 4247. (b) From  $\text{TiCl}_4$  mediated aldol reaction of cobalt complexed propinal, Mukai, C.; Kataoka, O.; Hanaoka, M. *Tetrahedron Lett.* **1991**, *32*, 7553.

- For example, 2-pyridyl thioester can be utilized in the synthesis of thioester (RSH, base), peptide ( $\text{RNH}_2$ , base), lactone ( $\text{Hg}^{2+}$ ,  $\text{Ag}^+$ ,  $\text{Cu}^+$ , or  $\text{Cu}^{2+}$ ), lactame and so on, or the resolution by  $\text{Ti}(\text{OPr}^t)_4$ .
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- In general, the *syn* isomers feature smaller  $\text{CHOH}$   $J$  values. Also,  $\text{CHOH}$  resonates at lower field in *syn* than in *anti* isomers.
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## Regioselective Synthesis of 2-Amino-3-cyanofuran Derivatives and Its Guanidine Cyclization Reaction

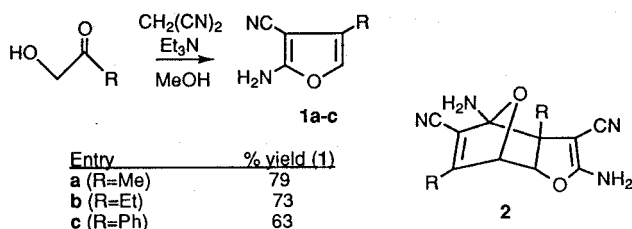
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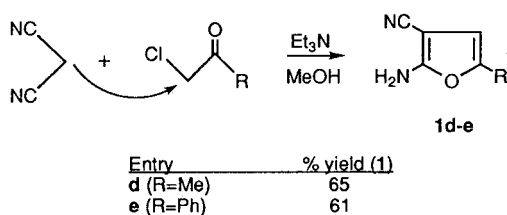
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It is reported that acylloins reacted with malononitrile in aqueous base to give 2-amino-3-cyanofuran derivatives.<sup>1</sup> The regioselective synthesis of 4- or 5-substituted-2-amino-3-cyanofuran was interested for the synthesis of pyrrolo[2,3-d]pyrimidine based anti tumor reagents.<sup>2</sup>

For the synthesis of 4-substituted-2-amino-3-cyanofuran,  $\alpha$ -hydroxy ketone was reacted with malononitrile in triethyl-



Scheme 1.



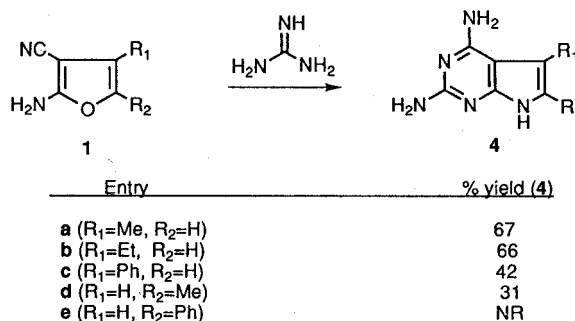
Scheme 2.

amine-methanol system (Scheme 1). Expected furan **1a-c** and the unexpected dimer **2** were obtained in reasonable yield as a 4:1 ratio respectively. The dimer **2** was formed by way of a Diels-Alder cycloaddition of **1** with itself. McKee<sup>3</sup> has reported that the dimer **2** was the only product in his reaction condition. The monomer **1** and the dimer **2** were in equilibrium at reflux, which indicates that it was not necessary to separate the mixture for further reaction.

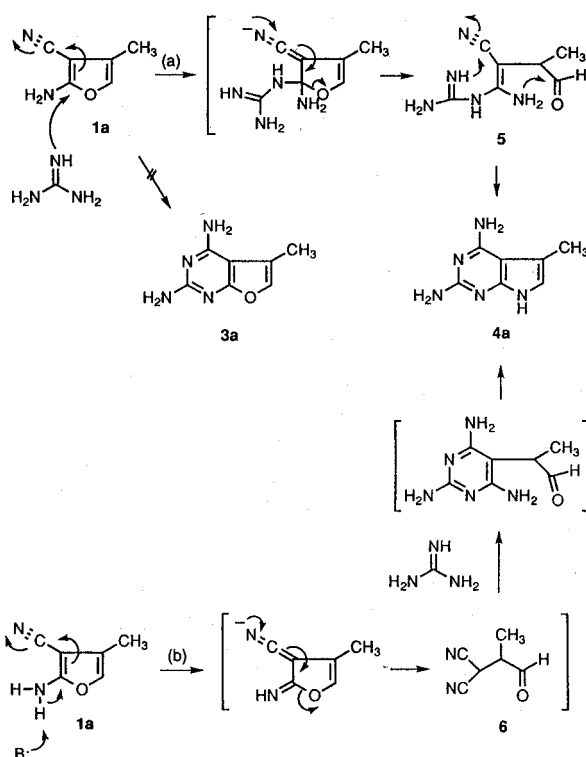
5-Substituted-2-amino-3-cyanofuran derivatives **1d-e** were also easily prepared from  $\alpha$ -chloro ketone and malononitrile (Scheme 2). Carbanion formed from malononitrile in basic condition attacked at  $\alpha$ -chloro carbon instead of carbonyl group to give 5-substituted furan, but attacked at carbonyl carbon in  $\alpha$ -hydroxy ketone to give 4-substituted furan (Scheme 1).

2-Amino-3-cyanofuran derivatives were utilized for the guanidine cyclization reaction. It has been thoroughly documented that *o*-aminonitriles can be readily cyclized to annulated 2,4-diaminopyrimidine systems by reaction with guanidine.<sup>4</sup> It was first explored the possible application of this well-known methodology to the preparation of a model 2,4-diaminofuro[2,3-*d*]pyrimidine **3a** by the reaction of guanidine with 2-amino-3-cyano-4-methylfuran **1a**, readily accessed by condensation of acetol (hydroxyacetone) with malononitrile. Surprisingly, the product of this reaction was shown to be 2,4-diamino-5-methylpyrrolo[2,3-*d*]pyrimidine **4a** rather than the anticipated furopyrimidine **3a**. This unexpected ring transformation/ring annulation reaction turned out to be fairly general (Scheme 3). Although substituents at position 4 of the furan ring can apparently be accommodated, small alkyl groups lead to better results than an aryl substituent. However, the reaction is sensitive to the presence and nature of substituents at position 5 and is blocked entirely by a 5-aryl substituent.

Plausible mechanisms for this guanidine mediated ring transformation/ring annulation reactions were shown in Scheme 4. In mechanism (a), initial Michael addition of the guanidine to the 2-position of the furan *o*-aminonitrile **1a** followed by furan ring cleavage could generate an open-chain carbonyl derivative **5**, which then recycles to an interme-



Scheme 3.



Scheme 4.

diate pyrrole, thus incorporating the 2-amino group of **1a** as the pyrrole NH grouping. Subsequent intramolecular addition of the guanidiny substituent to the *o*-substituted nitrile group then completes the pyrimidine ring annulation to give **4a**. In mechanism (b), deprotonation of the acidic 2-amino group of the starting furan *o*-aminonitrile **1a** by the strongly basic guanidine could be followed by C-O bond cleavage to generate an intermediate ketenimine which, by prototropic rearrangement, would lead to the substituted malononitrile **6**. Further reaction with the guanidine in the usual way would lead to a 2,4,6-triaminopyrimidine carrying a  $\beta$ -carbonyl substituent at C-5; final ring closure would form the fused pyrrole ring. In an attempt to elucidate the reaction pathway involved in this intriguing transformation as supported examples for mechanism (b) which only showed in thiophene derivatives,<sup>5</sup> the reaction of furan *o*-aminonitrile **1a** with NaOH only gave decomposition. But the supported examples<sup>6</sup> for mechanism (a) showed in all furan derivatives and thus mechanism (a) could be the more plausible route.

In summary, 4- or 5-substituted-2-amino-3-cyanofuran was selectively synthesized and was utilized for the synthesis of pyrrolo[2,3-d]pyrimidine via guanidine cyclization reaction.

Typical Procedure:

#### Synthesis of 2-Amino-3-cyano-4-methylfuran 1a.

Acetol (3.7 g, 50 mmol) was dissolved in methanol (20 mL) with stirring under an atmosphere of nitrogen and a mixture of malononitrile (3.5 g, 53 mmol) and triethylamine (6.96 mL, 50 mmol) in methanol (25 mL) was added slowly dropwise at such a rate as to maintain the reaction temperature below 40 °C. After 20 min., the reaction mixture was diluted with water (50 mL) and extracted with methylene chloride (2×50 mL). The organic layers were combined, dried (Na<sub>2</sub>SO<sub>4</sub>) and condensed to a brown solid. Recrystallization from ethyl acetate-hexane gave **1a** (4.8 g, 39.3 mmol, 79%) as pale yellow needles: mp 155-157 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 6.57 (s, 1H, =CH), 4.78-4.99 (br s, 2H, NH<sub>2</sub>), 2.01 (s, 3H, CH<sub>3</sub>).

**Synthesis of 2,4-Diamino-5-methylpyrrolo[2,3-d]pyrimidine 4a.** To a solution of guanidine free base (from 20 mmol of guanidine hydrochloride and 20 mmol of NaOMe) in anhydrous EtOH (50 mL) was added the aminonitrile **1a** (1.52 g, 10 mmol) and the mixture was refluxed for 36 h. The mixture was cooled in ice bath and the precipitated solid was filtered, washed with MeOH, and dried to give **4a** (720 mg, 4.1 mmole, 41%) as a white solid. The mother liquor was then concentrated under reduced pressure and the resulting precipitate was collected by filtration and dried to yield an additional 450 mg of pure **4a** as a white solid (overall yield 67%); mp 166-168 °C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 10.49 (s, 1H, NH), 6.40 (s, 1H, =CH), 6.30 (s, 2H, NH<sub>2</sub>), 5.40-5.75 (br s, 2H, NH<sub>2</sub>), 2.20 (s, 3H, CH<sub>3</sub>).

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## Convenient One-Pot Synthesis of Polystyrene Copolymer Containing Thiocarbamate Group

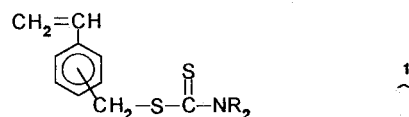
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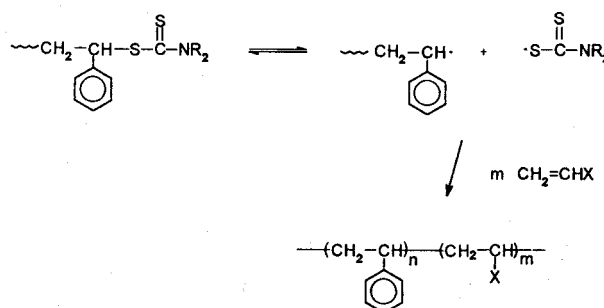
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Organic compounds containing dithiocarbamate group have been used extensively primarily for the vulcanization of rubbers. But they have received quite attention in radical polymerization because they can be applied to the synthesis of block and graft copolymers.<sup>1,2</sup> For example, by thermal or by UV activation, a polymer chain having a dithiocarbamate group is dissociated and generate two radicals; one is a polymeric radical and the other is a relatively stable thiocarbamate-radical as shown in Scheme 1. Activation of the dithiocarbamate functionalized polymer in the presence of a second monomer, therefore, generates block or graft copolymers.<sup>2,3</sup> During the polymerization the thiocarbamate radical caps the growing radical reversibly.

An easy preparation method of prepolymer containing dithiocarbamate group, therefore, has a significant meaning. There are a couple of ways to prepare prepolymer containing dithiocarbamate group depending on the location of the group on the polymer chain. Polymers with the pendant dithiocarbamate groups which are randomly distributed on the polymer chain have been prepared by copolymerization of a vinyl monomer containing dithiocarbamate<sup>2</sup> such as vinylbenzyl dithiocarbamate **1**.



In this report, however, a prepolymer containing dithiocarbamate was easily prepared for the first time by an one-pot synthesis as shown in Scheme 2. The second reaction step involves a polymer reaction which seems to be difficult to carry out. But this reaction led to facile conversion to the corresponding product.



Scheme 1.