SELECTIVE CARBOPHILIC ADDITION OF ORGANOLITHIUMS TO THIOAMIDES. A NOVEL SYNTHESIS OF UNSYMMETRICAL KETONES AND  $\alpha$ -ALKYLATED AMINES

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Summary: Thioamides, readily available from aldehydes, sulfur and secondary amines, can be converted to unsymmetrical ketones by the *carbo*philic addition of organolithiums to the thiocarbonyl group. Reduction of the intermediates with lithium aluminum hydride gives  $\alpha$ -alkylated or  $\alpha$ -arylated amines.

Many efforts have been directed to discover new synthetic methods of unsymmetrical ketones from readily available starting materials in search of efficient and easy manipulation.<sup>1</sup> In an extension of the studies on the application of thioamides to organic synthesis,<sup>2,3</sup> we have disclosed herein that thioamides react with organolithiums in a *carbophilic* fashion selectively to afford a variety of unsymmetrical ketones in high yield, and, in addition, that treatment of the reaction mixture with lithium aluminum hydride gives the corresponding  $\alpha$ -alkylated or  $\alpha$ -arylated amines by the desulfurization.

Thiocarbonyl compounds such as thioketones and dithioesters generally undergo *thiophilic* addition by organometallic nucleophiles like Grignard reagents and organolithiums.<sup>4,5</sup> In sharp contrast, the present reaction provides an unprecedented example for the selective *carbophilic* addition of carbon nucleophiles into carbon-sulfur double bond of thioamides.

At first several examples for the preparation of a variety of ketones (3) are summarized in Table 1.<sup>6</sup> Phenylthiomorpholide (1a) reacts with phenyllithium (2c) very smoothly in ether at room temperature in a *carbo*philic mode to give benzophenone cleanly in 81 % yield after acid hydrolysis. Insufficient hydrolysis of the reaction mixture affords a blue solution of thiobenzophenone involving the desired ketone. Thus it should be noted that thioketones can be also isolated by controlling hydrolysis conditions.<sup>7</sup> Similarly, alkyllithium such as methyllithium (2a) and n-butyllithium (2b) can also enter the reaction to afford the corresponding unsymmetrical ketones (3).

|       | 1.  | R <sup>2</sup> -Li (2)             |                  |                    |  |
|-------|---|------------------------------------|------------------|--------------------|--|
|       | $R^1 - C - NR_2$  |                                    | ➤ R <sup>1</sup> | $-C-R^2$           |  |
|       | <u> </u>  | dil. HCl                           |                  | Ö (3)              |  |
| Entry | 7 Thioamide (1)   | Organolithi                        | um (2)           | % Yield of $3^{b}$ |  |
| 1     | $C_{6}H_{5} \overset{C-N}{\parallel} $                                | CH3Li                              | (2a)             | 57                 |  |
| 2     | 1a  | n-C <sub>4</sub> H <sub>9</sub> Li | (2b)             | 76                 |  |
| 3     | 1a  | C <sub>6</sub> H <sub>5</sub> Li   | (2c)             | 81                 |  |
| 4     | C6H5C-NMe2  | 2b                                 |                  | 62                 |  |
|       | s (1b)  |                                    |                  |                    |  |
| 5     | 1b  | 2c                                 |                  | 55                 |  |
| 6     | p-ClC <sub>6</sub> H <sub>4</sub> C-N O                               | 2a                                 |                  | 65                 |  |
|       | s (1c)  |                                    |                  |                    |  |
| 7     | 1c  | 2c                                 |                  | 88                 |  |
| 8     | p-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> C-N O                 | 2a                                 |                  | 84                 |  |
|       | s (1d)  |                                    |                  |                    |  |
| 9     | 1d  | 2b                                 |                  | 71                 |  |
| 10    | 1d  | 2c                                 |                  | 67                 |  |
| 11    | p-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> C-N O                | 2a                                 |                  | 72                 |  |
|       | Š ── (1e)   |                                    |                  |                    |  |
| 12    | 1e  | 2b                                 |                  | 67                 |  |
| 13 g  | $^{O-(CH_3)_2NC_6H_4C-N}$   | 2c                                 |                  | 53                 |  |
|       | ŝ(1f)   |                                    |                  |                    |  |
| 14    | с <sub>6<sup>н</sup>5<sup>сн</sup>2<sup>с-й</sup> о</sub>             | 2c                                 |                  | 79                 |  |
|       | s(1g)   |                                    |                  |                    |  |
| 15    | p-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> C-N O | 2c                                 |                  | 57                 |  |
|       | s (1h)  |                                    |                  |                    |  |
| 16    | C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CH <sub>2</sub> C-N 0   | 2c                                 |                  | 67                 |  |
|       | s (1i)  |                                    |                  |                    |  |

Table 1. Reactions of thioamides with organolithiums<sup>a</sup>

<sup>a</sup>All reactions were conducted in ether at room temperature for 4 h. <sup>b</sup>Yield after isolation by TLC was shown. Yield was not always optimized.

material. Nucleophiles such as Grignard reagents, organocopper reagents, and organocuprates are not effective for the present reaction. Ether is the most suitable solvent among examined. Various aromatic thioamides similarly gave the corresponding unsymmetrical ketones (3).

Aliphatic thioamides, instead of aromatic ones, can be also converted to the corresponding unsymmetrical ketones by the reaction with aryllithium, although, with alkyllithium, thioenolates are formed, the ketones not being obtained.

The replacement of aldehydic hydrogen by an alkyl group is generally

attained by the introduction of carbon electrophiles into stabilized carbanions derived from protected aldehydes via the well-known umpolung method.<sup>8</sup> The whole conversion of the present synthesis of unsymmetrical ketones can be viewed formally as the substitution of the aldehydic hydrogen by a carbanion, since the starting thioamides can be readily prepared from aldehydes, sulfur and secondary amine.<sup>9</sup>

Next, we can achieve easily the synthesis of various amines by the reduction of the reaction mixture of organolithium and thioamides with lithium aluminum hydride, before the acid hydrolysis,  $\alpha$ -alkylated or  $\alpha$ -arylated amines (4) being obtained in high yield. The results are summarized in Table 2. Although alkylation of the  $\alpha$ -carbanion of amino derivatives has been demonstrated by using an electronically modified nitrogen function,<sup>10</sup> several serious drawbacks to this methodology still exist. On the contrary, the whole sequences of this conversion starting from secondary amines can be seen as the synthesis of tertiary amines in which N-alkylation followed by  $\alpha$ -alkylation or  $\alpha$ -arylation of secondary amines occurs.

In conclusion, this work demonstrates that thioamides undergo the attack of organolithiums on the carbon atom of carbon-sulfur double bond selectively. As a result, the synthetic utility of the present work was mostly displayed by the replacement of aldehydic hydrogen by alkyl and aryl groups, alkylation of secondary amines accompanying by  $\alpha$ -alkylation or  $\alpha$ -arylation, readily available starting materials, and simple and mild manipulation of the conversion.

General procedure is as follows. (A) n-Butyllithium in hexane (0.5 mmol) was added to the solution of an thioamide (0.25 mmol) in ether (10 ml) at room temperature. The resulting mixture was stirred for 4 h and 10 % hydrochloric acid (10 ml) was added and hydrolyzed at room temperature. After workup as usual, the solvent was removed by the evaporator and the product was separated by the preparative TLC (silica gel) using benzene as an eluent. (B) To a solution of thioamide (1.0 mmol) in ether, n-butyllithium (2 mmol) was added with stirring at room temperature. After stirring for 4 h, lithium aluminum hydride (10 mmol) was added carefully to the reaction mixture and the resulting mixture was heated at reflux for 4 h. After hydrolysis with 10 % sodium hydroxide under cooling with ice bath, the resulting solution was extracted with ether and the extract was worked up as usual. The residue showed to be almost pure by GLC and NMR analysis.

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1531

| $\mathbb{R}^{1} - \mathbb{C} - \mathbb{N}$                           | 1. R <sup>2</sup> -Li (2)                                    | R <sup>1</sup> R <sup>2</sup> CH-NO |
|--|--|-------------------------------------|
|  | 2. LiAlH <sub>4</sub><br>3. H <sub>2</sub> 0/OH <sup>-</sup> | (4)                                 |
| Entry Thioamide (1)  | Organolithium (2)  | Yield of amine (4) <sup>b,c</sup>   |
| $1 C_{6}H_{5}C-N O S (1a)$   | n-C <sub>4</sub> H <sub>9</sub> Li (2b)                      | 94                                  |
| 2 <b>1</b> a   | C <sub>6</sub> H <sub>5</sub> Li (2c)                        | 100 (72)                            |
| $3 p-CH_3C_6H_4C-N$  | 2b   | 96 (47)                             |
| $\begin{array}{c} 4  p-CH_3OC_6H_4C-N \\ \$ \qquad (1e) \end{array}$ | 2b   | (59)                                |

Table 2. Synthesis of  $\alpha$ -alkylated and  $\alpha$ -arylated amines.<sup>a</sup>

<sup>a</sup>All reactions were carried out in 1 mmol scale in ether. <sup>b</sup>Determined by GLC. Yield was not always optimized. <sup>C</sup>Yield after distillation by Kugelrohr is shown in parentheses.

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