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THE ADDITION OF 2-LITHIO PHENYLTHIOACETONITRILE TO α,β-UNSATURATED CYCLIC KETONES

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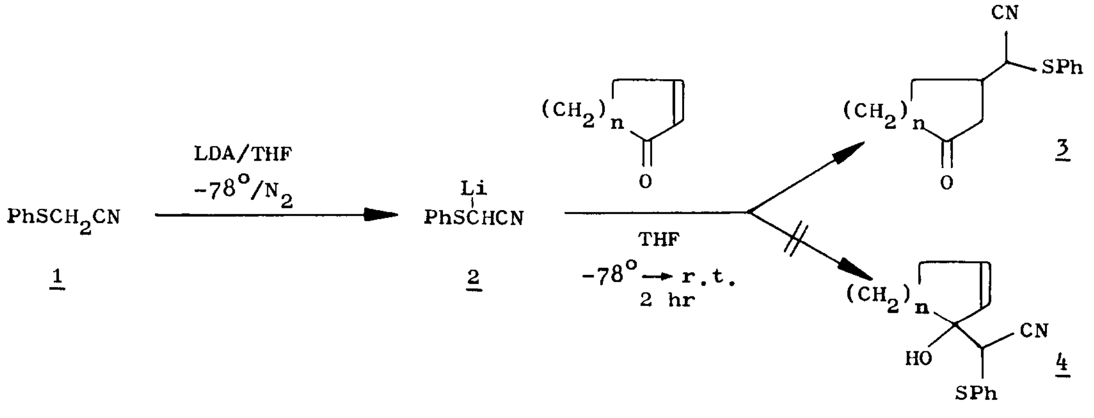
The Michael reaction is one of the most important processes in synthetic organic chemistry[1]. It provides the basis for the Robinson annelation and many other chain-elongation reactions[2]. If performed intramolecularly, the reaction becomes a valuable tool for the construction of complex ring systems[3]. The scope of the reaction is further expanded by the recent findings that organocuprates[4] and certain functional group-stabilized carbanions undergo exclusively 1,4-addition to α,β-unsaturated carbonyl systems[5]. Unfortunately, the number of established good "Michael donors" is quite limited. In many cases, the reaction gave either entirely 1,2-adducts[6] or a mixture of both adducts[7]. Furthermore, among the examples in which only 1,4-adducts are produced, some are not synthetically useful. Therefore the search for new and potentially useful Michael donors is highly desirable.

During the course of studies directed toward the total synthesis of anti-cancer sesquiterpenes, we had an opportunity to investigate the reaction between 2-lithio phenylthioacetonitrile (2) and 2-cyclopenten-1-one (n=1).



The lithium salt 2 was generated by slow addition of a THF solution of phenylthioacetonitrile (1)[8] to 1 equivalent of lithium diisopropylamide in THF at -78°C. Upon treatment with 2-cyclopenten-1-one under the conditions shown above, we found that the only addition product was the 1,4-adduct 3 (n=1) and no 1,2-adduct 4 (n=1) could be detected. However, when the temperature was kept at -78° throughout the reaction, substantial amount of 4 (n=1) was obtained (see Table 1). These results are in agreement with the observations made by Schultz and Yee on related systems[5j] that at lower temperature 1,2-adducts were formed by kinetic process, while at higher temperature, the thermodynamically-controlled 1,4-addition became the predominent process. We also found that at a given temperature, solvent change from THF to anhydrous ether caused a slight increase in the amount of 4 (n=1).

Having completed the cyclopentenone series, we then turned our attention to cyclohexenone (n=2) in order to evaluate the effects of ring-size on the product ratio. Thus, the lithium salt 2 was allowed to react with 2-cyclohexen-1-one under various conditions. Again we found that at room temperature, the adducts were exclusively those resulted from 1,4-addition, no matter which solvent was used. However, at -78° as much as 21% of the 1,2-adduct (4, n=2) was produced. In contrast to the 5-membered counterpart, much more 1,2-adduct was found when the reaction was carried out in ether instead of THF at -78°. The results are summerized in Table 1.

Table 1. The addition of 2-Lithio phenylthioacetonitrile to Cyclic Enones

Entry	n	Solvent	Reaction Time(hr)[a]	Reaction Temperature	Yield(%)	Ratio[b] of 1,4-	to 1,2-Adducts
1	1	THF	3	-78°	84	89	11
2	1	THF	2	rt	90	100	0
3	1	Ether	3	-78°	86	86	14
4	1	Ether	2	rt	79	98	2
5	2	THF	4	-78°	88	79	21
6	2	THF	2	rt	87	100	0
7	2	Ether	4	-78°	83	46	54
8	2	Ether	2	rt	93	100	0

a. It was found that after the specified reaction times the cycloalkenones were completely consumed.

b. The ratios of the 1,4- to 1,2-adducts were determined by PMR analysis of the chromatographed materials[10].

A representative experiment is described below:

To a solution of 2.18 mmol of LDA in dry THF (prepared from 221 mg of diisopropylamine, 2.2 ml of freshly-distilled THF, and 1.4 ml of 15% n-BuLi in hexane) at -78^{o} under nitrogen was added, *via* a syringe, a solution of 325 mg (2.18 mmol) of phenylthioacetonitrile in 0.5 ml of THF. The resulting clear solution was stirred for 5 min and a solution of 179 mg (2.18 mmol) of 2-cyclopenten-1-one in 0.5 ml of THF was added dropwise. After the addition was complete, the mixture was stirred at -78^{o} for 5 min. The acetone-dry ice bath was then removed and the reaction mixture was allowed to warm to room temperature. After stirring was continued for 2 hr, the reaction was quenched by adding 10% hydrochloric acid until slightly acidic to litmus paper. The mixture was poured into 5 ml of water and the aqueous mixture was extracted with ether (6 ml x 3). The combined ether extracts were washed with brine (2 ml x 1), dried over anh. $MgSO_4$, and rotary-evaporated to give 456 mg (90% yield) of a viscous liquid The crude product was chromatographed (silica-gel column, hexane/EtOAc=5:1) and subjected to PMR analysis.

The structures of the 1,4-adducts (**3**, n=1 and 2) were established by spectral analyses of the chromatographed materials obtained from entry 2 and 6, respectively.

Compound **3** (n=1): IR (neat): 4.45, 5.75, 13.30, and 14.40 cm^{-1}; PMR ($CDCl_3$) δ 3.82 (t, 1H, J=7.0 Hz); MASS m/e 231(M^+).

Compound **3** (n=2): IR (neat): 4.45, 5.85, 13.30, and 14.40 cm^{-1}; PMR ($CDCl_3$) δ 3.68 and 3.77 (2d, 1H, J=7.0 Hz); MASS m/e 245(M^+).

Attempted isolations of the 1,2-adducts (entry 3 and 7) by chromatography failed. However, if the reaction mixtures were quenched with acetic anhydride before the usual work-up, the resulted acetate and enol acetate in each of the mixtures were separable over silica gel. Thus, the alcohols (**4**, n=1 and 2) were characterized as their acetates. Compound **4** (n=1) acetate: IR (neat): 4.45, 5.75, 6.10, 13.3 and 14.5 cm^{-1}; PMR ($CDCl_3$) δ 2.02 (s. 3H), 4.86 and 5.03 (2s, 1H), 6.00 and 6.21 (2m, 2H); MASS m/e 273(M^+), 213(M^+-CH_3COOH).

Compound **4** (n=2) acetate: IR (neat): 4.45, 5.75, 6.10, 13.30, and 14.40 cm^{-1}; PMR ($CDCl_3$) δ 2.02 (s, overlapped with the ring protons), 4.92 and 5.06 (2s, 1H) 6.08 (br.s, 2H); MASS m/e 287(M^+), 227(M^+-CH_3COOH).

Finally, by slight modification of the product structures, the reactions described herein would provide a simple and efficient synthetic method for the preparation of highly functionallized ring systems. The application of this method to the synthesis of biologically important substances is being actively persued in our laboratories.

Acknowledgement

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References and Notes

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8) This compound was prepared by a modified procedure of Dijkstra and Backer[9]. Thus, thiophenol was treated with chloroacetonitrile in the presence of one equivalent of triethyl amine for 30 min at room temperature. The average yield was about 80%

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