THE REACTION OF O-ETHYL SUCCINIMIDE WITH ARYLLITHIUM COMPOUNDS : AN EFFICIENT METHOD FOR THE INTRODUCTION OF 3-ETHOXYCARBONYL-PROPIONYL GROUP TO AROMATIC COMPOUNDS

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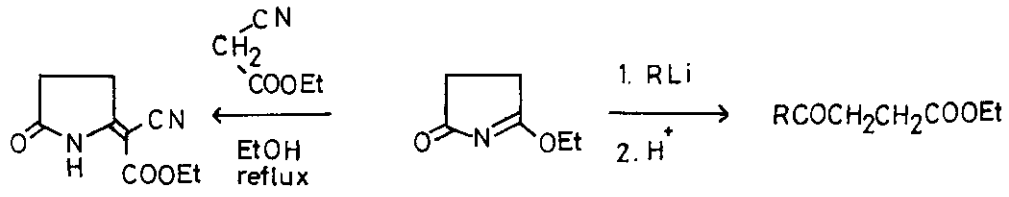
Abstract -- O-Ethyl succinimide (I) was found to be an efficient reagent for the introduction of 3-ethoxycarbonylpropionyl group ($-COCH_2CH_2COOEt$) to aromatic compounds by a single operation under mild conditions.

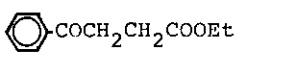
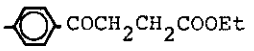
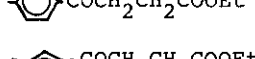
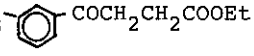
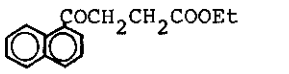
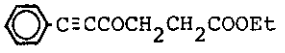
In the previous communication[1], we have demonstrated synthetically useful reactions of O-ethyl succinimide (I)[2] with primary and secondary amines, especially o-aminophenylcarbonyl derivatives affording quinazolones and quinazolines in good yields. In this paper we wish to report an efficient synthetic method for the introduction of 3-ethoxycarbonylpropionyl group to aromatic compounds by the use of O-ethyl succinimide (I) and aryllithium compounds.

It has been reported that the reaction of I with active methylene compounds such as ethyl cyanoacetate and ethyl acetoacetate gave 5-alkylidene-2-pyrrolidones (II)[3]. We attempted to apply this reaction to other nucleophiles. In this process, it was found that the reaction of I with aryllithium gave directly ethyl 4-aryl-4-oxobutyrate (III) in moderate yields. Several examples are listed in Table. We also found that lithium acetylide reacted with I to give III (Run 6).



II I III

Table. Reaction of I with Aryllithium (or Lithium Acetylide)*1

Run	Starting Material	Product*2	Isolated*3 Yield (%)	bp*4 (or mp) (°C)
1	bromobenzene		67	132 (2 mmHg)
2	p-dibromobenzene		69	(57-58)
3	p-bromochloro-benzene		69	(56-57)
4	m-bromotoluene		54	110 (1 mmHg)
5	1-bromonaphthalene		67	157-160 (1 mmHg)
6	phenylacetylene		40	130 (1 mmHg)

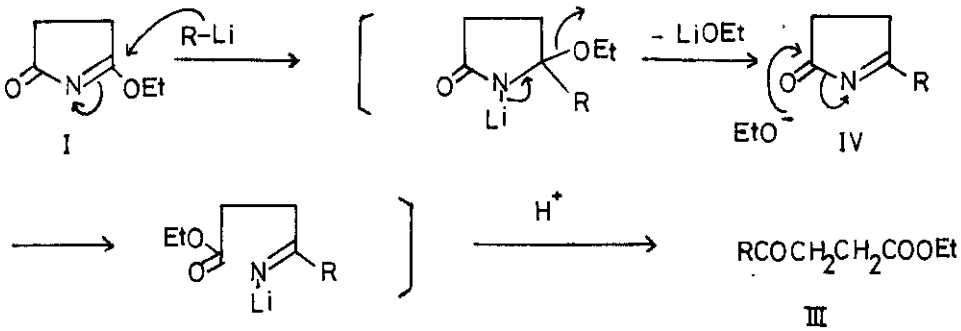
*1 Organolithium compounds were prepared by mixing of starting materials and n-BuLi in ether at 0° for 15 min.

*2 All products gave satisfactory analytical results and spectral data.

*3 Yields have not been optimized.

*4 Bp is the bath temperature of Kugelrohr.

The mechanizm for this reaction is proposed as follows : Nucleophilic attack of the



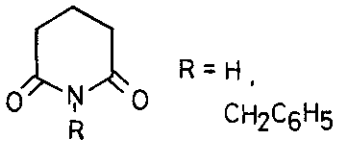
ethoxide anion generated from the addition-elimination reaction would take place at the carbonyl carbon of intermediate (IV) to give ketoester (III) after the cleavage of C-N bond and acidic work-up.

A typical procedure is described for the synthesis of ethyl 3-benzoylpropionate (Run 1) :

A solution of n-BuLi (3.3 mmol) was added at 0° to a solution of bromobenzene (3

mmol) in 5 ml of dry ether under argon. After stirring at 0° for 15 min, a solution of I (3 mmol) in 2 ml of dry ether was added at -78°. The reaction mixture was stirred at -78° for 1 h and then at room temperature for 1 h. By usual work-up, chromatography, and distillation, a pure colorless oil was obtained in 67% yield.

In conclusion, it is noted that this reagent (I) is useful and convenient for the direct introduction of 3-ethoxycarbonylpropionyl group on the lithiated position of aromatic compounds by a single operation under mild conditions. This method could overcome the disadvantage of Friedel-Crafts acylation[4] which is not always selective for aromatic substitution reactions. As it is reported[5] that glutarimides (V), homologs of succinimide, reacted with phenyllithium to give 6-hydroxy-6-phenyl-2-oxopiperidines, the reaction of I with aryllithium, different from the reaction of real imides, provides an alternative utility.



V

Research on the scope and limitation of this reaction is currently being investigated.

REFERENCES AND NOTE

1. T. Nagasaka, F. Hamaguchi, N. Ozawa, and S. Ohki, Heterocycles, 1978, 9, 1375.
2. This material (bp 112°/2 mmHg), prepared from Ag salt of succinimide and EtI by the method of literature [K. Matoba and T. Yamazaki, Chem. Pharm. Bull. (Tokyo), 1974, 22, 2999] is stable for at least several months by the storage under argon in the refrigerator.
3. T. Yamazaki, K. Matoba, S. Imoto, and T. Terashima, Chem. Pharm. Bull. (Tokyo), 1976, 24, 3011.
4. K. Shudo, Yuki Gosei Kagaku Kyokai Shi, 1978, 36, 425 and references cited therein.
5. J. T. Wrobel, J. Cybulski, and Z. Dabrowski, Synthesis, 1977, 686.

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