

**N-CARBOETHOXYPIPERIDINE, A CONVENIENT REAGENT FOR THE
PREPARATION OF SYMMETRICAL KETONES FROM
ORGANOLITHIUMS¹**

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Dedicated to Prof. Rolf Huisgen on the occasion of his 75th birthday

Abstract - *N*-Carboethoxypiperidine on reaction with organolithium reagents, RLi, followed by acidic work-up gave excellent yields of the corresponding symmetrical ketones, R₂CO.

INTRODUCTION

A convenient aldehyde synthesis procedure was developed using *N*-formylpiperidine.² The method has been extended for the general preparation of aldehydes and ketones using *N,N*-dimethylformamide and related amides.³ The topic has been reviewed.⁴ An efficient procedure for the preparation of ketones from *N*-methoxy-*N*-methyamides was also developed by Nahm and Weinreb.⁵ However, the procedure requires multi-step sequence for the preparation of symmetrical ketones. We have now discovered an extremely convenient one step procedure for the preparation of symmetrical ketones by reacting organolithiums with *N*-carboethoxypiperidine.

RESULTS AND DISCUSSION

The synthesis of ketones from acyl halides, anhydrides, carboxylic acid esters or amides using various organometallics has been extensively investigated over the past few decades.⁶ When the organometallic compound is a Grignard reagent or an organolithium, ketones are obtained only in low yields because the initially formed ketone reacts with a second molecule of RMgX or RLi to give the addition product.⁶ Low temperatures,⁷ use of HMPA solvent,⁸ and inverse addition have been used to increase the yield of ketone.⁹ Amides generally give better yields of ketone at room temperature compared to other substrates. Reaction of organometallics with chloroformates also result in overaddition products. An alternative for the synthesis of symmetrical ketones using *N,N*-disubstituted carbamates or carbamoyl chloride had earlier been reported.¹⁰⁻¹² However, in these studies, the investigations were limited to the preparation of a few aromatic ketones. Preparation of symmetrical ketones using *N*-carboethoxypiperidine is efficient and simple and the reaction pathway is depicted in Scheme I. *N*-Carboethoxypiperidine is readily prepared through the addition of piperidine to commercially available ethyl chloroformate. Organolithium reagents, RLi , on reaction with *N*-carboethoxypiperidine in ether followed by acidic work-up, gave excellent yields of the corresponding symmetrical ketones (Table I). The reaction can be carried out under mild conditions ($0\text{ }^{\circ}\text{C}$ to $30\text{ }^{\circ}\text{C}$). No tertiary alcohol by-products were found due to addition of excess organolithiums. However, the reaction did not work in the case of strongly basic and sterically bulky *tert*-butyllithium and only the corresponding *tert*-butylated amide could be isolated. Furthermore, in the case of Grignard reagents, the yields of the symmetrical ketones were comparatively low, indicating competing side reactions due to electron transfer.

Scheme 1

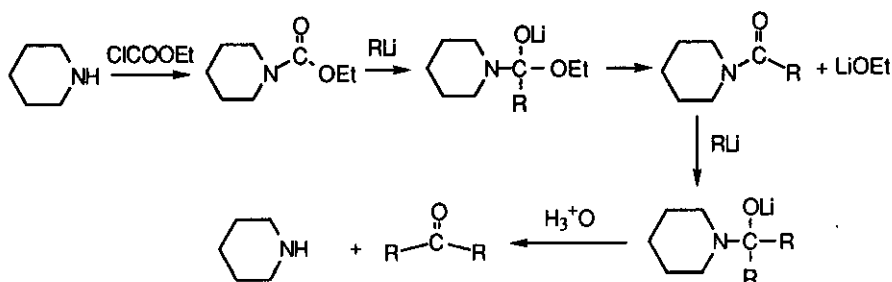
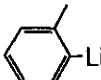
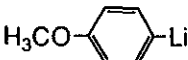
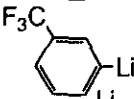
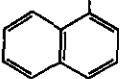
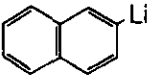
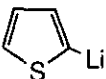


Table I. One-pot Synthesis of symmetrical ketones*

Lithium Reagent	Isolated Yield (%)	mp°C Found	or bp°C _(bath) /Torr Reported	Ref.
	95	47	49	14a
	82	71	72	14b
	74	111	110	14b
	75	141	142	14a
	82	100	101	14c
	86	102	104	14b
	92	124	125	14b
	75	90	90	14b
	84	75/30	72/33	14d
	87	85/19	88/22	14b
	85	161	162	14b

* All the products reported are known in the literature and were adequately characterized by ^1H , ^{13}C nmr, and GC-ms.

The presently developed method using *N*-carboethoxypiperidine compliments existing methods for the preparation of symmetrical ketones. The method is highly convenient and when needed piperidine can be recovered after work-up.

Preparation of *N*-Carboethoxypiperidine:

To a stirred solution of ethyl chloroformate (100 ml) in 500 ml ether at -78 °C, under nitrogen, piperidine (200 ml) was added dropwise. After completion of the addition, the cooling bath was removed. The reaction mixture was stirred at room temperature for 1 h and refluxed for another hour, followed by addition of water (100 ml). The ether layer was separated and washed with water (2x50 ml). The organic layer was dried over sodium sulfate, the solvent was evaporated and the residue was distilled in vacuum to give pure *N*-carboethoxypiperidine¹³ (bp 211-212 °C, 760 mm, yield 95%)

Preparation of symmetrical ketones, General procedure:

A solution of *N*-carboethoxypiperidine (10 mmol) in 20 ml ether was slowly added to the corresponding freshly prepared organolithium¹⁵ (25 mmol) in 20 ml of ether at 0 °C under nitrogen over a period of 5 min. The mixture was then brought to room temperature and stirred for 30 min followed by reflux for another 30 min. Subsequently, the reaction mixture was quenched with 3 N HCl. The product was extracted with diethyl ether (3x50 ml), and the ether layers were combined and washed with water (150 ml), aqueous sodium hydrogen carbonate solution (100 ml), and saturated sodium chloride solution (150 ml). After drying the ether layer with anhydrous magnesium sulfate, the solvent was evaporated to provide the symmetrical ketone which was further purified by recrystallization or distillation (Purity of compounds $\geq 98\%$ by ¹H and ¹³C-nmr and tlc.)

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15. The organolithium was prepared by treating the corresponding bromide with 2.1 equivalent of powdered lithium metal (obtained from Aldrich) in ether under reflux.

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