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CONVENIENT KETONE SYNTHESIS VIA N-ACYLAZIRIDINES

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ABSTRACT: N-Acylaziridines couple efficiently with organolithium and Grignard reagents to produce ketones in high yields.

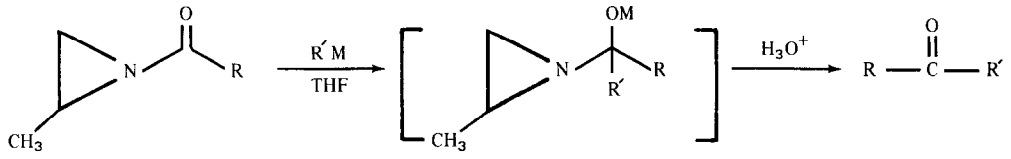
Many reports on the synthesis of ketones from organometallic reagents and carboxylic acid derivatives have appeared.[1]

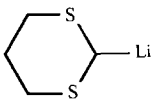
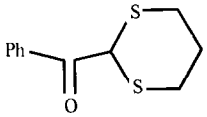
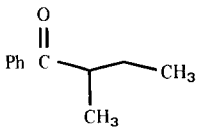
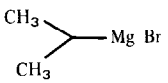
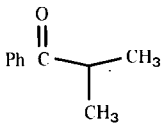
The preparation of ketones by the reaction of organolithium reagents with simple carboxamides has been reported.[2] However, though certain aromatic amides react smoothly in this process to give ketones in good yields, the reaction with aliphatic amides is not an efficient process.[2c,d] In addition, it was found that the reaction was limited to primary alkyllithiums.[2b]

Meyers and Comins reported the utility of N-methylamino pyridyl amides as efficient acylating agents for Grignard reagents.[3] Recently, Nahm and Weinreb reported that N-methyoxy-N-methylamides react in good yields with organolithium and Grignard reagents to give ketones.[4]

We have found that N-acylaziridines react cleanly with both organolithium and Grignard reagents in THF to form ketones in high yields. Some of our results are shown in the table.

As the table indicates, various ketones can be synthesized by this method. The reaction works well with both aliphatic and aromatic acylaziridines, including the highly hindered t-butyl compound, which are readily prepared. Significantly, the reaction is not limited to primary organolithium reagents, the N-acylaziridines react effectively with secondary organolithiums, secondary Grignard reagents, and 2-lithiodithianes.[5]



R	R'M	Reaction Conditions	Product	Isolated Yield (%)
CH_3	$CH_3(CH_2)_4C{\equiv}CLi$	0° → r.t.	$CH_3(CH_2)_4C{\equiv}C\,C(=O)\,CH_3$	75
	$CH_3(CH_2)_4C{\equiv}C$ Mg Br	0° → r.t.		70
	PhLi	0°	Ph C(=O) CH_3	77
	Ph Mg Br	0°		75
t-Bu	$CH_3(CH_2)_4C{\equiv}CLi$	0° → r.t.	$CH_3(CH_2)_4C{\equiv}C\,C(=O)\,Bu^t$	70
	PhLi	0°	Ph C(=O) Bu^t	82
Ph	n BuLi	0°	Ph C(=O) Bu^n	80
	N BuLi (2 eq)	0°		77
	Et Mg Br	0°	Ph C(=O) Et	80
		-20° → 0°		73
	Sec-BuLi	0° → r.t. (2 h)		81
		0° → r.t. (2 h)		75

Product yields are high if reactions are run with a slight excess of organometallic reagents. No significant amounts of over-addition products and other side products[6] have been detected in the example listed. In addition, these reactions do not require the stringent experimental conditions crucial to the success of many other methods.[1,3]

We believe that the chemistry described here provides a general and efficient method for the synthesis of ketones.

Preparation of N-Acylaziridines. In a typical procedure: To a solution of propyleneimine[7] (5.7 g, 0.1 mol) and triethylamine (11.1 g, 0.11 mol) in petroleum ether[8] (30 ml) at 0°C, was added a solution of acid chloride (0.1 mol) in petroleum ether (20 ml) dropwise slowly over 30 min. After complete addition, the mixture was stirred at 0°C for an additional 15 min. Then, the mixture was diluted with petroleum ether (~100 ml) and the white solid of triethylamine hydrochloride salt was removed by filtration. The clear filtrate was concentrated and the residue (only one spot by TLC) was purified by distillation in vacuo to give the pure product in 60-80% yields.

General Procedure for Preparation of Ketones. To a solution of N-acylaziridine (2.0 mmol) in dry THF (5 ml) at the desired temperature was added the organometallic reagent (2.2 mmol) dropwise. The reaction mixture was stirred at the indicated temperature until TLC (ether-petroleum ether, 1:1) showed no starting material, usually less than 1 h. Aqueous HCl (5%) was added slowly followed by ether extraction. The organic layer was washed with water, brine, dried (Na_2SO_4) and concentrated to give the product, purified by chromatography (ether-petroleum ether, 1:1).

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(5) For a discussion on acylation of 2-lithiodithiane, see: D. Seebach and E.J. Corey, J. Org. Chem., 1975, 40, 231.

(6) For nucleophilic ring opening of activated aziridines, see: H. Stamm, P. Assithianakis, B. Buchholz and R. Weib, Tetrahedron Lett., 1982, 23, 5021.

(7) (a) Commercially available from Fluka Chemical Corp.

(b) Because of the hazardous nature of propyleneimine, all work should be conducted in a well-ventilated hood.

(8) We found that for preparation of these N-acylaziridines, petroleum ether (bp 30-60°C) is a superior solvent to methylene chloride, chloroform or benzene.

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