

An Effective Method for the Regio- and Stereo-selective 1,4-Addition to β -Cyclopropyl- α,β -enones using Organocopper(I)-Aluminium Trichloride Reagents

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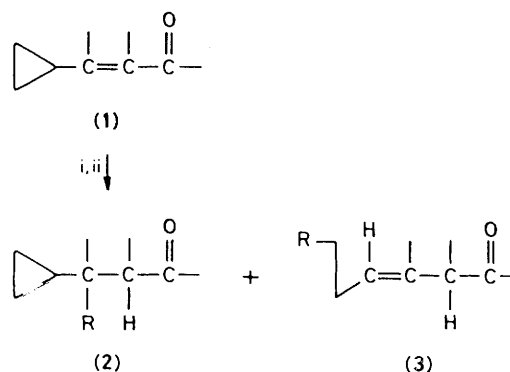
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An efficient regio- and stereo-selective 1,4-addition to β -cyclopropyl- α,β -enones using $\text{RCu}-\text{AlCl}_3$ is described.

The 1,4-addition of ordinary organocopper(I) reagents, such as the Gilman reagent (R_2CuLi), to α,β -unsaturated carbonyl compounds has proved highly useful in organic synthesis.^{1,2} With β -cyclopropyl- α,β -enones, however, the conventional organocopper(I) reagent has a serious limitation. While the conjugate addition to an α,β -enone proceeds well, addition to a β -cyclopropyl- α,β -enone (1) [to yield compound (2)] is in significant competition with cyclopropane ring opening [yielding the product (3)], in particular when steric factors cause the cyclopropyl group to be approximately perpendicular to the plane of the enone system, and this latter reaction may even dominate (Scheme 1).³⁻⁸

Although 1,4-adducts (2) of β -cyclopropyl- α,β -enones are promising intermediates for the synthesis of many cyclopropane ring-containing natural products, scanning the literature revealed that no general method for the efficient regio- and stereo-selective 1,4-addition to such enones was available.

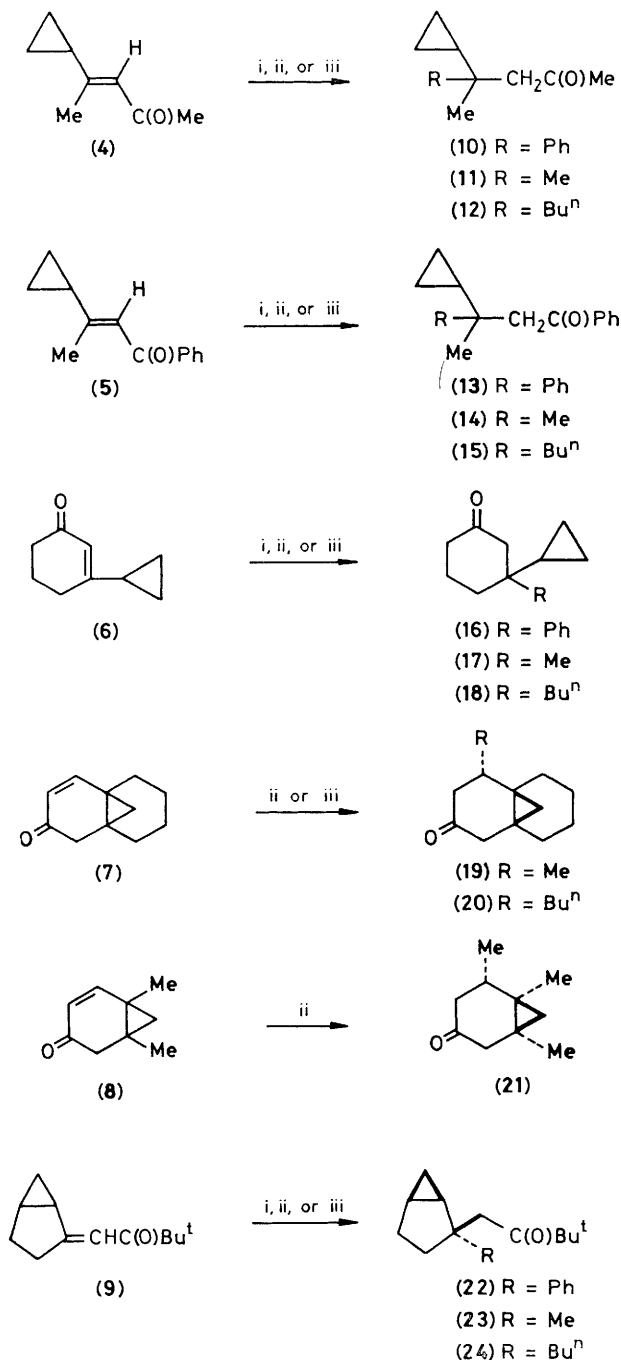
We report that an equimolar mixture of an organocopper(I) compound and aluminium trichloride ($\text{RCu}-\text{AlCl}_3$) is an effective reagent for the regio- and stereo-selective 1,4-



Scheme 1. Reagents: i, R_2CuLi ; ii, H_3O^+ .

addition to β -cyclopropyl- α,β -enones. In the absence of AlCl_3 , stoichiometric organocopper reagents (RCu) are inactive for 1,4-addition to β -cyclopropyl- α,β -enones. The results in

Table 1 show that RCu-AlCl_3 gives 1,4-adducts in satisfactory yields. It has been reported that the enones (7) and (8) give a mixture of the 1,4-adduct and by-product(s) formed after cyclopropane ring-opening on treatment with Me_2CuLi .^{4,5} In contrast, both the enones (7) and (8) gave the regio- and stereo-selective adducts (19) and (21), respectively, after treatment with 5 mol. equiv. of MeCu-AlCl_3 . In these reactions, we did not detect any cyclopropane ring-opening by gas chromatographic analysis and ^1H n.m.r. measurements of the products. The stereochemistry of the adducts (19) and (21) was ascertained by comparison of observed spectral data with those of authentic spectra.^{4,5} The difference in reactivity of Me_2CuLi and MeCu-AlCl_3 was also worthy of remark.



Scheme 2. Reagents: i, PhCu-AlCl_3 ; ii, MeCu-AlCl_3 ; iii, $\text{Bu}^n\text{Cu-AlCl}_3$.

Table 1. Yields of products in the reactions of β -cyclopropyl- α,β -enones with RCu-AlCl_3 .^a

Expt.	Substrate	Reagent ^b	1,4-Adduct, yield/%
1	(4)	i	(10) 84
2	(4)	ii	(11) 82
3	(4)	iii	(12) 86
4	(5)	i	(13) 87
5	(5)	ii	(14) 98
6	(5)	iii	(15) 92
7	(6)	i	(16) 84
8	(6)	ii	(17) 98
9	(6)	iii	(18) 95
10	(7)	ii	(19) 75
11	(7)	iii	(20) 57
12	(8)	ii	(21) 72
13	(9) ^c	i	(22) 70
14	(9) ^c	ii	(23) 89 ^d
15	(9) ^c	iii	(24) 87 ^d

^a Because the RCu-AlCl_3 reagent is a heterogeneous suspension, complete formation of the 1,4-adduct was obtained by using 5 mol. equiv. of RCu-AlCl_3 . All reactions were carried out at least in duplicate and the following procedure for the 1,4-addition is typical. To a stirred suspension of MeCu (2.8 mmol) in dry ether (10 ml) under Ar at -70°C was added dropwise a solution of AlCl_3 (2.8 mmol) in ether (2 ml) and the mixture was stirred for 1 h. The enone (9) (100 mg, 0.56 mmol) in dry ether (6 ml) at -70°C was added to the mixture with stirring, and the temperature was gradually raised to -50°C . After the usual work-up, the product was purified, if necessary, by silica gel column chromatography to yield the pure adduct (23) (96 mg, 89% yield after Kugelrohr distillation). ^b Reagents are designated as in Scheme 2. Other organocopper(I) reagents such as $\text{RCu-Bu}_3\text{P}$ gave unsatisfactory results for the present 1,4-addition. ^c The enone (9) is a ca. 1:1 mixture of (*E*)- and (*Z*)-stereoisomers. ^d The stereochemistry of (23) and (24) was inferred from ^1H n.m.r. spectra.

Whereas Me_2CuLi was quite reluctant to undergo the 1,4-addition with the enone (9), MeCu-AlCl_3 readily reacted with (9) at -70°C to yield the adduct (23) as the sole product in a high yield.[†]

The present methodology for the 1,4-addition to β -cyclopropyl- α,β -enones using RCu-AlCl_3 has several advantages over the ordinary organocopper(I) reagent in terms of stereo- and regio-selectivity, and of efficiency.

We thank Professor J. A. Marshall and Professor C. P. Casey for providing us with the authentic spectra of (19) and (21) respectively.

Received, 15th March 1982; Com. 294

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[†] All new compounds exhibited satisfactory spectroscopic and analytical data consistent with the proposed structures.